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L73 ANSWER 1 OF 53 MEDLINE
AN 2000074454 MEDLINE
DN 20074454 PubMed ID: 10608742
TI **Dose**-dependent response to **IFN-gamma** in muscle flap microcirculation.
AU Turegun M; Gudemez E; Yang L; DeCorleto P; Siemionow M
CS Department of Plastic and Reconstructive Surgery, Gulhane Military Medical Academy, Ankara, Turkey.
SO JOURNAL OF RECONSTRUCTIVE MICROSURGERY, **(1999 Nov)** 15 (8) 605-8.
Journal code: 8502670. ISSN: 0743-684X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124
AB In this study, the authors attempted to determine the effects of intraarterial administration of various **doses** of **Interferon-gamma (IFN-gamma)** on microcirculation in a rat muscle flap model. In Group 1 (control), 0.6 ml vehicle solution-PBS-BSA, in Group 2 0.6 ml **IFN-gamma** (25 ng/ml), in Group 3 0.6 ml **IFN-gamma** (50 g/ml), in Group 4 0.6 ml **IFN-gamma** (100 g/ml), were injected. The diameter of the cremaster arterioles and venules, red blood cell velocities, the number of rolling leukocytes and lymphocytes, sticking leukocytes and lymphocytes, capillary perfusion, and endothelial edema index were evaluated. Deterioration of flow hemodynamics was confirmed by a significant decrease in flow velocity in the main artery (A1) (47 percent in Group 3 and 65 percent in Group 4). All **dosages** of **IFN-gamma** caused a statistically significant decrease in rolling leukocytes, but this effect was more obvious in the 25 ng/ml group. Injury to the vascular endothelium was confirmed by a two-fold increase in transmigrating leukocytes in the 100 ng/ml group. This was accompanied by 60 percent and 75 percent drops in capillary perfusion, and by 12 percent and 24 percent drops in the endothelial edema index in Groups 3 and 4, respectively. The results indicate that direct intraarterial administration of **IFN-gamma** in **doses** higher than 25 ng/ml may be toxic to muscle flaps.
CT Check Tags: Animal; Comparative Study
Disease Models, Animal
Dose-Response Relationship, Drug
Injections, Intra-Arterial
***Interferon Type II: AD, administration & dosage**
Microcirculation: DE, drug effects
Rats
Rats, Sprague-Dawley

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Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
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Reconstructive Surgical Procedures: MT, methods
Reference Values
Regional Blood Flow: DE, drug effects
*Surgical Flaps: BS, blood supply
RN **82115-62-6 (Interferon Type II)**

L73 ANSWER 2 OF 53 MEDLINE
AN 1999279982 MEDLINE
DN 99279982 PubMed ID: 10353542
TI Effects of immunomodulation with **interferon-gamma** on hepatic ischemia-reperfusion injury.
AU Langdale L A; Wilson L; Jurkovich G J; Liggitt H D
CS Department of Surgery, University of Washington, Seattle 98195, USA.
SO SHOCK, **(1999 May)** 11 (5) 356-61.
Journal code: 9421564. ISSN: 1073-2322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990803
AB The development of an **inflammatory** response after injury depends on the participation of a variety of cell populations and endogenous mediators. **Interferon-gamma** (**IFN-gamma**) is a potent cellular immunomodulating cytokine that contributes to **acute** and chronic **inflammation**. In this study, the effects of immunomodulation on ischemia-reperfusion injury were examined using increasing doses of recombinant, rabbit-specific **IFN-gamma** in an in situ model of hepatic ischemia-reperfusion. Pretreatment with **low dose** **IFN-gamma** augmented injury as measured by histology, aminotransferase concentrations, and myeloperoxidase activity. By contrast, high dose **IFN-gamma** pretreatment, equivalent to **IFN-gamma** supplements used in clinical trials, resulted in a lack of **neutrophil** infiltration and minimal progression of late phase, **neutrophil**-mediated reperfusion injury. These results suggest that immunomodulating mediators such as **IFN-gamma** may play a regulating role in the evolution of ischemia-reperfusion, contributing to the development and resolution of **acute** hepatic injury.
CT Check Tags: Animal; Support, U.S. Gov't, Non-P.H.S.
*Adjuvants, Immunologic: TU, therapeutic use
Alanine Transaminase: BL, blood
Aspartate Aminotransferases: BL, blood
Dose-Response Relationship, Drug
***Interferon-gamma, Recombinant: TU, therapeutic use**
*Liver: BS, blood supply
Mice
Mice, Inbred C57BL
***Reperfusion Injury: DT, drug therapy**
CN 0 (Adjuvants, Immunologic); **0 (Interferon-gamma, Recombinant)**;
EC 2.6.1.1 (Aspartate Aminotransferases); EC 2.6.1.2 (Alanine Transaminase)

L73 ANSWER 3 OF 53 MEDLINE
AN 1999244921 MEDLINE
DN 99244921 PubMed ID: 10228031
TI Ischemia/reperfusion-induced **IFN-gamma** up-regulation: involvement of IL-12 and IL-18.
AU Daemen M A; van't Veer C; Wolfs T G; Buurman W A
CS Department of General Surgery, University of Maastricht, The Netherlands.

SO JOURNAL OF IMMUNOLOGY, **(1999 May 1)** 162 (9) 5506-10.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199905
ED Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990520

AB Tissue injury as a consequence of ischemia followed by reperfusion is characterized by early as well as late signs of inflammation. The latter, among others, involves **IFN-gamma**-dependent up-regulation of MHC class I and II Ag expression. Employing a murine model of renal ischemia, we show that renal IL-18 mRNA up-regulation coincides with caspase-1 activation at day 1 following ischemia. **IFN-gamma** and IL-12 mRNA are subsequently up-regulated at day 6 following ischemia. Combined, but not separate, in vivo neutralization of the **IFN-gamma** inducing cytokines IL-12 and IL-18 reduces **IFN-gamma**-dependent MHC class I and II up-regulation to a similar extent as **IFN-gamma** neutralization, suggesting the involvement of functional IL-12, IL-18, and **IFN-gamma** protein. These results reveal a novel relationship between tissue injury of nonmicrobial origin and the induction of IL-12 as well as IL-18. The collaboration observed between endogenous IL-12 and IL-18 in the induction of **IFN-gamma** after renal ischemia/reperfusion, resembles the immune response to bacterial infections.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Antibodies, Monoclonal: AD, administration & dosage
Cell Movement: IM, immunology
Histocompatibility Antigens Class I: BI, biosynthesis
Histocompatibility Antigens Class II: BI, biosynthesis
Inflammation: IM, immunology
***Interferon Type II: PH, physiology**
Interleukin-12: BI, biosynthesis
Interleukin-12: IM, immunology
*Interleukin-12: PH, physiology
Interleukin-18: BI, biosynthesis
Interleukin-18: IM, immunology
*Interleukin-18: PH, physiology
*Ischemia: IM, immunology
Ischemia: ME, metabolism
Ischemia: PP, physiopathology
*Kidney: BS, blood supply
Kidney: IM, immunology
Kidney: PP, physiopathology
Mice
Neutrophils: IM, immunology
Neutrophils: PA, pathology
***Reperfusion Injury: IM, immunology**
Reperfusion Injury: ME, metabolism
Reperfusion Injury: PP, physiopathology
Time Factors
*Up-Regulation: IM, immunology
RN 187348-17-0 (Interleukin-12); **82115-62-6 (Interferon Type II)**
CN 0 (Antibodies, Monoclonal); 0 (Histocompatibility Antigens Class I); 0 (Histocompatibility Antigens Class II); 0 (Interleukin-18)

L73 ANSWER 4 OF 53 MEDLINE
AN 1998445899 MEDLINE
DN 98445899 PubMed ID: 9772722
TI Echinococcus multilocularis infection in mice: in vivo treatment with a

low dose of **IFN-gamma** decreases
metacestode growth and liver fibrogenesis.
AU Liance M; Ricard-Blum S; Emery I; Houin R; Vuitton D A
CS Laboratoire de Parasitologie, Faculte de Medecine, Creteil, France.
SO PARASITE, **(1998 Sep)** 5 (3) 231-7.
Journal code: 9437094. ISSN: 1252-607X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981207
AB As no antiparasitic drug is definitively efficient in patients with alveolar echinococcosis, the effects of exogenous **IFN-gamma** on murine Echinococcus multilocularis infection were assessed with regards to the parasite burden, parasite-specific immune responses, and the urinary level of the collagen cross-link pyridinolines. They were analyzed after 3-week treatments with 1 or 5 micrograms of **IFN-gamma** per day twice a week. The treatment with 1 microgram transiently reduced the liver metacestode load, and the metastase weight as far as 6 weeks after the end of treatment. It slightly increased Th 1-type T cell responses and reduced the excretion of pyridinolines. These results should encourage further study to assess whether the decrease in liver fibrosis leads to an improvement of the efficacy of albendazole therapy. In contrast, the treatment with 5 micrograms increased the liver metacestode load and was less efficient than that with 1 microgram in decreasing pyridinoline excretion. These results incitate to follow up carefully patients with alveolar echinococcosis who are treated with **IFN-gamma**.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Amino Acids: UR, urine
Antibodies, Helminth: BI, biosynthesis
Disease Models, Animal
Dose-Response Relationship, Drug
***Echinococcosis, Hepatic: DT, drug therapy**
Echinococcus: IM, immunology
Echinococcus: IP, isolation & purification
Hypersensitivity, Delayed
Immunoglobulin G: BI, biosynthesis
Interferon-gamma, Recombinant: AD, administration & dosage
***Interferon-gamma, Recombinant: TU, therapeutic use**
Liver: PS, parasitology
Liver: PA, pathology
Mice
Mice, Inbred AKR
Organ Weight
RN 63800-01-1 (pyridinoline)
CN 0 (Amino Acids); 0 (Antibodies, Helminth); 0 (Immunoglobulin G); **0 (Interferon-gamma, Recombinant)**

L73 ANSWER 5 OF 53 MEDLINE
AN 1998236920 MEDLINE
DN 98236920 PubMed ID: 9576006
TI Nasal tolerance to experimental autoimmune myasthenia gravis: tolerance reversal by nasal administration of minute amounts of **interferon -gamma**.
AU Li H L; Shi F D; Bai X F; Huang Y M; van der Meide P H; Xiao B G; Link H
CS Division of Neurology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden.
SO CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, **(1998 Apr)** 87 (1) 15-22.

Journal code: 0356637. ISSN: 0090-1229.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
ED Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980518
AB Tolerance to **B cell**-mediated experimental autoimmune myasthenia gravis (EAMG), an animal model for myasthenia gravis (MG) in humans, can be achieved by nasal administration of the autoantigen acetylcholine receptor (AChR). Nasal tolerance induction requires only 1/1000 of the amount of AChR used for oral tolerance induction, but is as effective in preventing EAMG. To investigate whether nasally induced tolerance to EAMG can be influenced by nasal administration of cytokines, recombinant rat **IFN-gamma** (total 5000 U/rat), a combination of AChR and **IFN-gamma** or AChR alone was given nasally to Lewis rats before immunization with AChR and complete Freund's adjuvant (CFA). One additional group of rats received the same amount of AChR nasally in conjunction with **IFN-gamma** (total 5000 U/rat) intraperitoneally. AChR given alone nasally induced effective tolerance to EAMG whereas rats receiving AChR + **IFN-gamma** by the nasal route exhibited a similar disease pattern, and similarly escalated T and **B cell** responses to AChR when compared to control EAMG rats. In contrast, administration of **IFN-gamma** i.p. together with AChR nasally did not affect the induction of tolerance to EAMG. **IFN-gamma** given alone nasally did not affect clinical EAMG. This study demonstrates that nasal tolerance can be modulated by nasal administration of minute amounts of **IFN-gamma**. Nasal administration of certain cytokines with beneficial effects might broaden the effectiveness of applying nasal tolerance as a potential therapeutic means of preventing autoimmune diseases.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Administration, Intranasal
Antibody Affinity
Autoantibodies: IM, immunology
Dose-Response Relationship, Drug
Dose-Response Relationship, Immunologic
*Immune Tolerance: DE, drug effects
Immunity, Mucosal
Immunoglobulin Isotypes: IM, immunology
***Interferon Type II: AD, administration & dosage**
Lymphocyte Transformation
***Myasthenia Gravis: IM, immunology**
Myasthenia Gravis: PC, prevention & control
Rats
Rats, Inbred Lew
*Receptors, Nicotinic: IM, immunology
RN **82115-62-6 (Interferon Type II)**
CN 0 (Autoantibodies); 0 (Immunoglobulin Isotypes); 0 (Receptors, Nicotinic)

L73 ANSWER 6 OF 53 MEDLINE
AN 1998152206 MEDLINE
DN 98152206 PubMed ID: 9491506
TI Immune responses to V antigen of Yersinia pestis co-encapsulated with **IFN-gamma**: effect of **dose** and formulation.
AU Griffin K F; Conway B R; Alpar H O; Williamson E D
CS Department of Pharmaceutical and Biological Sciences, Aston University, Birmingham, UK.
SO VACCINE, **(1998 Mar)** 16 (5) 517-21.
Journal code: 8406899. ISSN: 0264-410X.

CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980415
AB Induction of systemic immune responses after intraperitoneal inoculation of poly(L)lactide microspheres containing the V antigen of Yersinia pestis co-encapsulated with **IFN-gamma** were investigated. Serum antibody responses and T cell proliferative responses were measured in groups of Balb/c mice which were injected intraperitoneally with single or double emulsion preparations of either V/**IFN-gamma** or V alone in a range of **dose** levels. Groups which received V antigen co-encapsulated with **IFN-gamma** produced higher V-specific antibody responses, predominantly of the IgG1 isotype. Administration of 25 micrograms V/**IFN-gamma** in a single emulsion resulted in a significantly increased ($p < 0.05$) splenic T cell proliferative response to V antigen compared with other formulations. It was concluded that **IFN-gamma** co-encapsulated with V antigen in poly(L)lactide microspheres acted as an adjuvant and increased antigen specific systemic immune responses. Therefore, co-encapsulation with **IFN-gamma** may result in effective single **dose** vaccines by increasing the immunogenicity of the formulations.
CT Check Tags: Animal; Female
*Antibodies, Bacterial: BI, biosynthesis
*Antigens, Bacterial: IM, immunology
B-Lymphocytes: IM, immunology
Chemistry, Pharmaceutical
Dose-Response Relationship, Drug
Drug Compounding
Injections, Intraperitoneal
***Interferon Type II: AD, administration & dosage**
Mice
Mice, Inbred BALB C
T-Lymphocytes: IM, immunology
***Yersinia pestis: IM, immunology**
RN **82115-62-6 (Interferon Type II)**
CN 0 (Antibodies, Bacterial); 0 (Antigens, Bacterial)

L73 ANSWER 7 OF 53 MEDLINE
AN 97361660 MEDLINE
DN 97361660 PubMed ID: 9218621
TI Myeloid differentiation treatment to diminish the presence of immune-suppressive CD34+ cells within human head and neck squamous cell carcinomas.
AU Young M R; Wright M A; Pandit R
CS Research Service, Hines Veterans Affairs Hospital, IL 60141, USA.
NC CA45080 (NCI)
CA48080 (NCI)
SO JOURNAL OF IMMUNOLOGY, **(1997 Jul 15)** 159 (2) 990-6.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199708
ED Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970805
AB Within human head and neck squamous cell carcinomas (HNSCC) that produce

granulocyte-macrophage CSF are CD34+ cells that exhibit natural suppressive (NS) activity. The present study aimed to identify how these NS cells mediate suppression and how to diminish their presence. CD34+ cells that were immunomagnetically isolated from fresh surgical HNSCC specimens produced a soluble product that blocked normal T cell stimulation through the TCR/CD3 complex. This inhibitory activity could be neutralized with Abs to TGF-betal. Since prior studies showed that the CD34+ NS cells within HNSCC cancers are myelomonocytic progenitor cells, the feasibility of using cytokines that can induce myeloid cell differentiation to diminish the presence of CD34+ NS cells was tested. Adding **low doses** of 100 U/ml **IFN-gamma** plus 10 U/ml TNF-alpha to bulk cultures of dissociated HNSCC cancers diminished the frequency of CD34+ cells. Studies with CD34+ cells that were isolated from the HNSCC cancers showed that this cytokine treatment induced differentiation of the CD34+ cells predominantly into **monocytic** cells. The consequence of treating CD34+ NS cells with the myeloid differentiation treatment was the loss of suppressive activity, a decline in TGF-beta production, and the production of TNF-alpha by the resulting **monocytic** cells. In HNSCC bulk cultures containing high levels of CD34+ NS activity, **IFN-gamma**/TNF-alpha not only reduced CD34+ cell levels, but also increased the capacity of the intratumoral T cells to express the p55 IL-2R. These studies show that **IFN-gamma**/TNF-alpha can induce differentiation of TGF-beta-secreting CD34+ NS cells into nonsuppressive **monocytic** cells that secrete TNF-alpha.

CT Check Tags: Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Antigens, CD34: IM, immunology
Carcinoma, Squamous Cell: IM, immunology
***Carcinoma, Squamous Cell: PA, pathology**
Cell Differentiation: DE, drug effects
Head and Neck Neoplasms: IM, immunology
***Head and Neck Neoplasms: PA, pathology**
***Hematopoietic Stem Cells: DE, drug effects**
Hematopoietic Stem Cells: IM, immunology
Hematopoietic Stem Cells: PA, pathology
*Immunosuppression
***Interferon Type II: PD, pharmacology**
***Leukocytes: IM, immunology**
Leukocytes: PA, pathology
Tumor Cells, Cultured
*Tumor Necrosis Factor: PD, pharmacology
RN **82115-62-6 (Interferon Type II)**
CN 0 (Antigens, CD34); 0 (Tumor Necrosis Factor)

L73 ANSWER 8 OF 53 MEDLINE
AN 97275153 MEDLINE
DN 97275153 PubMed ID: 9129047
TI Dose-dependent enhancements by **interferon-gamma** on functional responses of **neutrophils** from chronic granulomatous disease patients.
AU Ahlin A; Elinder G; Palmblad J
CS Department of Pediatrics, The Karolinska Institute at Sachs' Children's Hospital, Stockholm, Sweden.
SO BLOOD, **(1997 May 1)** 89 (9) 3396-401.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199706

ED Entered STN: 19970612
Last Updated on STN: 19970612
Entered Medline: 19970603

AB **Interferon-gamma (IFN-gamma)** is recommended as prophylaxis against infections in patients with chronic granulomatous disease (CGD). However, since the optimal dose, the dosing interval, and the mechanisms of action are not well-defined, we studied the effects on CGD **neutrophil** (PMN) functions ex vivo of **interferon-gamma (IFN-gamma)**.
Evaluations were made on oxidative capacity, measured by superoxide anion production and chemiluminescence after stimulation with f-met-leu-phe (f-MLP) or phorbol-myristate-acetate, the killing of Aspergillus fumigatus hyphae (assessed as conversion of the tetrazolium salt MTT to formazan), and on the expression of Fc gammaRI receptor (CD64). After randomization, 9 CGD patients (4 with gp91phox, 3 with p47phox, 1 with p67phox deficiency and 1 with unspecified CGD) were given **IFN-gamma**, either 50 or 100 microg/m2 subcutaneously on 2 consecutive days after double blinded randomization. Furthermore, one female hyperlyonized X-linked carrier with a CGD phenotype was also studied separately after **IFN-gamma** treatment. Evaluations were made the day before and on days 1, 3, 8, and 18 after **IFN-gamma** administration. The killing of A fumigatus hyphae, being close to zero before **IFN-gamma**, was enhanced on day 3, being 36% higher than pretreatment values in the high-dose CGD group and 17% in the **low-dose** group. The expression of Fc gammaRI on PMN increased 3.7-fold in the high-dose and 2.3-fold in the **low-dose** CGD group, being maximal on day 1. Oxidative functions were raised in only selected patients represented by different subtypes of CGD. The hyperlyonized carrier of X-linked CGD responded to **IFN-gamma** with more enhanced oxidative responses and Aspergillus killing of her PMNs than the other patients. This study suggests that a higher dose of **IFN-gamma** than currently recommended confers transient enhancements of certain PMN functions in CGD patients.

CT Check Tags: Female; Human; In Vitro; Male; Support, Non-U.S. Gov't
Adolescence
Adult
Aspergillus
Chemiluminescence
Child
Dose-Response Relationship, Drug
Double-Blind Method
Granulomatous Disease, Chronic: BL, blood
Granulomatous Disease, Chronic: GE, genetics
***Granulomatous Disease, Chronic: TH, therapy**
Interferon-gamma, Recombinant: PD, pharmacology
***Interferon-gamma, Recombinant: TU, therapeutic use**
Kinetics
Membrane Glycoproteins: DF, deficiency
N-Formylmethionine Leucyl-Phenylalanine: PD, pharmacology
NADH Dehydrogenase: DF, deficiency
NADPH Dehydrogenase: DF, deficiency
Neutrophils: DE, drug effects
***Neutrophils: PH, physiology**
Phagocytosis: DE, drug effects
Phosphoproteins: DF, deficiency
Superoxides: BL, blood
Tetradecanoylphorbol Acetate: PD, pharmacology
Time Factors

RN 11062-77-4 (Superoxides); **126805-82-1 (neutrophil cytosol factor 47k)**; 16561-29-8 (Tetradecanoylphorbol Acetate); 59880-97-6 (N-Formylmethionine Leucyl-Phenylalanine)

CN **0 (Interferon-gamma, Recombinant)**; 0 (Membrane Glycoproteins); 0 (Phosphoproteins); 0 (X-CGD protein); 0 (**neutrophil** cytosol

factor 67K); EC 1.6.99.1 (NADPH Dehydrogenase); EC 1.6.99.3 (NADH Dehydrogenase)

L73 ANSWER 9 OF 53 MEDLINE
AN 97053320 MEDLINE
DN 97053320 PubMed ID: 8897832
TI Potentiation by thyroxine of **interferon-gamma**-induced antiviral state requires PKA and PKC activities.
AU Lin H Y; Thacorf H R; Davis F B; Davis P J
CS Department of Medicine, Albany Medical College, New York, USA.
SO AMERICAN JOURNAL OF PHYSIOLOGY, **(1996 Oct)** 271 (4 Pt 1) C1256-61.
Journal code: 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961216
AB Added to HeLa cells previously exposed to recombinant human **interferon (IFN)-gamma** for 20 h, thyroid hormone [L-thyroxine (T4)] in physiological concentrations potentiates the antiviral action of **IFN-gamma** by more than 100-fold in 4 h. We examined protein kinase activities for their contributions to the mechanism of this posttranslational effect of thyroid hormone. Added concurrently with thyroid hormone, the protein kinase C (PKC) inhibitor CGP-41251 (5 nM) blocked T4 potentiation of **IFN-gamma** action. Coincubated with CGP-41251, phorbol 12-myristate 13-acetate (PMA) reversed the effect of the inhibitor on thyroid hormone action. U-73122 (10 nM), a phospholipase C inhibitor, also blocked hormone potentiation. KT-5720 (500 nM), a protein kinase A (PKA) inhibitor, completely inhibited the T4 effect, whereas 8-bromoadenosine 3',5'-cyclic monophosphate (8-BrcAMP) restored hormone action in the presence of KT-5720. In the absence of T4, 8-BrcAMP and PMA, added together to cells in the 4-h paradigm, fully reproduced hormone potentiation of the antiviral effect of **IFN-gamma**. Incubated individually with **IFN-gamma**-treated cells, the two agonists had no potentiating action. Thyroid hormone apparently must activate both PKA and PKC in the nongenomic pathway of **IFN-gamma** action to enhance antiviral activity in HeLa cells.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Calmodulin: PD, pharmacology
Cyclic AMP: PH, physiology
Cyclic AMP-Dependent Protein Kinases: AI, antagonists & inhibitors
*Cyclic AMP-Dependent Protein Kinases: PH, physiology
Dose-Response Relationship, Drug
Drug Synergism
Enzyme Inhibitors: PD, pharmacology
Estrenes: PD, pharmacology
Hela Cells
Indoles: PD, pharmacology
***Interferon Type II: AD, administration & dosage**
L Cells (Cell Line)
Mice
Protein Kinase C: AI, antagonists & inhibitors
*Protein Kinase C: PH, physiology
Pyrroles: PD, pharmacology
Pyrrolidinones: PD, pharmacology
***Rhabdoviridae Infections: PP, physiopathology**
Staurosporine: AA, analogs & derivatives

Staurosporine: PD, pharmacology
Sulfonamides: PD, pharmacology
Tetradecanoylphorbol Acetate: PD, pharmacology
***Thyroxine: AD, administration & dosage**
Time Factors
Vesicular stomatitis-Indiana virus
*Viral Interference: DE, drug effects

RN 108068-98-0 (KT 5720); 112648-68-7 (U 73122); 120685-11-2 (4'-N-benzoylstaurosporine); 16561-29-8 (Tetradecanoylphorbol Acetate); 60-92-4 (Cyclic AMP); 62996-74-1 (Staurosporine); 65595-90-6 (W 7); 7488-70-2 (Thyroxine); **82115-62-6 (Interferon Type II)**

CN 0 (Calmodulin); 0 (Enzyme Inhibitors); 0 (Estrenes); 0 (Indoles); 0 (Pyrroles); 0 (Pyrrolidinones); 0 (Sulfonamides); EC 2.7.1.- (Protein Kinase C); EC 2.7.10.- (Cyclic AMP-Dependent Protein Kinases)

L73 ANSWER 10 OF 53 MEDLINE
AN 96225880 MEDLINE
DN 96225880 PubMed ID: 8635194
TI **Low-dose**-melphalan-induced up-regulation of type-1 cytokine expression in the s.c. tumor nodule of MOPC-315 tumor bearers and the role of **interferon gamma** in the therapeutic outcome.
AU Gorelik L; Mokyr M B
CS Department of Biochemistry (M/C 536), University of Illinois at Chicago 60680, USA.
NC CA54413 (NCI)
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1995 Dec)** 41 (6) 363-74.
Journal code: 8605732. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960719
Last Updated on STN: 19970203
Entered Medline: 19960705
AB We have previously shown the importance of endogenous tumor necrosis factor (TNF) production for the curative effectiveness of **low-dose** melphalan (L-phenylalanine mustard) for mice bearing a large MOPC-315 tumor. In the current study we demonstrate that **low-dose** melphalan is actually associated with enhanced expression of mRNA for TNF alpha in the s.c. tumor nodule. Moreover, the expression of mRNA for **interferon gamma** (**IFN gamma**) and interleukin-12 (IL-12; p40) is also elevated at the tumor site. However, while elevation in the expression of mRNA for TNF alpha and **IFN gamma** is evident within 24 h after the chemotherapy, elevation in the expression of mRNA for IL-12(p40) is first evident 72 h after the chemotherapy. Moreover, neutralizing anti-**IFN gamma** mAb, like neutralizing anti-TNF mAb but not neutralizing anti-IL-12 mAb, reduced the curative effectiveness of **low-dose** melphalan for MOPC-315 tumor bearers. Studies into the mechanism through which **IFN gamma** mediates its antitumor effect in **low-dose**-melphalan-treated MOPC-315 tumor-bearing mice revealed that MOPC-315 tumor cells, which are not sensitive to the direct antitumor effects of TNF, display some sensitivity to the antiproliferative activity of high concentrations of **IFN gamma**. However, unlike TNF alpha, **IFN gamma** is unable to promote the generation of anti-MOPC-315 cytotoxic T lymphocyte activity and, in fact, exerts an inhibitory activity on CTL generation. Taken together, our studies illustrate that **low-dose** melphalan therapy of MOPC-315 tumor bearers is associated with the rapid elevation in the expression of mRNA for **IFN gamma** and TNF, two cytokines which are important for

the curative effectiveness of **low-dose** melphalan, and which mediate their antitumor effect, in part, through distinct mechanisms.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antineoplastic Agents, Alkylating: AD, administration & dosage
*Antineoplastic Agents, Alkylating: PD, pharmacology
Antineoplastic Agents, Alkylating: TU, therapeutic use
Base Sequence
Cytotoxicity, Immunologic: DE, drug effects
*Gene Expression Regulation, Neoplastic: DE, drug effects
Injections, Subcutaneous
Interferon Type II: AI, antagonists & inhibitors
Interferon Type II: BI, biosynthesis
Interferon Type II: GE, genetics
***Interferon Type II: PH, physiology**
Melphalan: AD, administration & dosage
*Melphalan: PD, pharmacology
Melphalan: TU, therapeutic use
Mice
Mice, Inbred BALB C
Molecular Sequence Data
Neoplasm Transplantation
Plasmacytoma: IM, immunology
Plasmacytoma: ME, metabolism
Plasmacytoma: PA, pathology
***Plasmacytoma: TH, therapy**
Polymerase Chain Reaction
RNA, Messenger: BI, biosynthesis
RNA, Messenger: GE, genetics
Stimulation, Chemical
***T-Lymphocytes, Cytotoxic: DE, drug effects**
T-Lymphocytes, Cytotoxic: IM, immunology
Tumor Cells, Cultured
*Tumor Necrosis Factor: BI, biosynthesis
Tumor Necrosis Factor: GE, genetics

RN 148-82-3 (Melphalan); **82115-62-6 (Interferon Type II)**

CN 0 (Antineoplastic Agents, Alkylating); 0 (RNA, Messenger); 0 (Tumor Necrosis Factor)

L73 ANSWER 11 OF 53 MEDLINE

AN 96160913 MEDLINE

DN 96160913 PubMed ID: 8570128

TI Augmentation of antitumor efficacy by the combination of actinomycin D with tumor necrosis factor-alpha and **interferon-gamma** on a melanoma model in mice.

AU Lasek W; Wankowicz A; Kuc K; Feleszko W; Giermasz A; Jakobisiak M

CS Department of Immunology, Institute of Biostructure, Medical School of Warsaw, Poland.

SO ONCOLOGY, **(1996 Jan-Feb)** 53 (1) 31-7.
Journal code: 0135054. ISSN: 0030-2414.

CY Switzerland

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199603

ED Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960306

AB The efficacy of combination treatment with actinomycin D (Act D), recombinant human tumor necrosis factor-alpha (TNF-alpha), and recombinant murine **interferon-gamma** (**IFN-gamma**) was examined on established MmB16 melanoma in mice. TNF-alpha alone had

marginal effect in vitro on melanoma cells. However, when this cytokine was combined with either Act D or **IFN-gamma**, synergistic cytostatic/cytotoxic effects were observed. The highest cytotoxicity was demonstrated in cultures of melanoma cells in which all three agents together were added. In mice inoculated with 10(6) melanoma cells (into the footpad of the hind limb) and treated locally with Act D, TNF-alpha and **IFN-gamma**, beneficial therapeutic effects were found. When initiated 1 week after tumor cell inoculation, the 7-day treatment with all these agents administered together at daily **doses**: 0.2 microgram (Act D), 1 microgram (TNF-alpha), and 200 U (**IFN-gamma**) resulted in a significant delay of tumor progression in comparison to the therapy that included either Act D alone or TNF-alpha in combination with **IFN-gamma**. Side effects of such a treatment, both local and systemic, were negligible. The results of this study demonstrate that combination of regional chemotherapy (actinomycin D) and immunotherapy (TNF-alpha/**IFN-gamma**) may display higher efficacy than either treatment alone and may increase therapeutic index without augmenting toxic effects.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Cell Survival: DE, drug effects
***Dactinomycin: AD, administration & dosage**
Dose-Response Relationship, Drug
***Interferon Type II: AD, administration & dosage**
***Melanoma, Experimental: DT, drug therapy**
Mice
Mice, Inbred C57BL
Mice, Inbred DBA
Recombinant Proteins
***Tumor Necrosis Factor: AD, administration & dosage**

RN 50-76-0 (Dactinomycin); **82115-62-6 (Interferon Type II)**

CN 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Recombinant Proteins); 0 (Tumor Necrosis Factor)

L73 ANSWER 12 OF 53 MEDLINE

AN 96103953 MEDLINE

DN 96103953 PubMed ID: 8543278

TI Roles of Mac-1, endogenous TNF-alpha, and **IFN-gamma** in pathogenesis of hepatic warm ischemia-reperfusion injury.

AU Tamura M

CS First Department of Surgery, Hokkaido University School of Medicine, Sapporo, Japan.

SO HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL SCIENCE, **(1995 Sep)** 70 (5) 717-28.
Journal code: 17410290R. ISSN: 0367-6102.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)

LA Japanese

FS Priority Journals

EM 199602

ED Entered STN: 19960227
Last Updated on STN: 19960227
Entered Medline: 19960214

AB The roles of neutrophil Mac-1 (CD11b/18) adhesion molecule, TNF-alpha and **IFN-gamma** in hepatic warm ischemia-reperfusion injury (IRI) were investigated with a newly established mouse model. Blood supply to the left lateral and the median lobe of the liver was interrupted with an atraumatic clip for 50 minutes. From 1 hour to 24 hours after reperfusion, TNF-alpha in the ischemic liver tissue was detected. **IFN-gamma** was not detected in ischemic liver tissue and blood. Pretreatment with anti-mouse Mac-1 monoclonal antibody (mAb) diminished the plasma GPT level, area of necrosis, and number of myeloperoxidase positive cells in ischemic liver lobe at 24 hours after

reperfusion. Pretreatment with anti-mouse TNF-alpha or anti-mouse **IFN-gamma** mAb did not affected any parameters. From these results, Mac-1 was considered to play an important role in a hepatic warm IRI. However, TNF-alpha and **IFN-gamma** were not considered to play a pivotal role in the pathogenesis of the injury and in the regulation of the neutrophils adhesion via Mac-1.

CT Check Tags: Animal; Male
English Abstract
***Interferon Type II: PH, physiology**
*Ischemia: ET, etiology
*Liver: BS, blood supply
*Macrophage-1 Antigen: PH, physiology
Mice
Mice, Inbred Strains
***Reperfusion Injury: ET, etiology**
*Tumor Necrosis Factor: PH, physiology

RN **82115-62-6 (Interferon Type II)**

CN 0 (Macrophage-1 Antigen); 0 (Tumor Necrosis Factor)

L73 ANSWER 13 OF 53 MEDLINE

AN 95348411 MEDLINE

DN 95348411 PubMed ID: 7622767

TI Antigen presenting cell-independent cytokine and spontaneous in vitro IgE production in patients with atopic dermatitis: increased **interferon-gamma** production and lack of effects of in vivo **low-dose interferon-gamma** treatment.

AU Simon M R; Cooper K D; Norris R B; Blok B; King C L

CS Department of Medicine, Wayne State University School of Medicine, Detroit, Allen Park, USA.

SO JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, **(1995 Jul)** 96 (1) 84-91.
Journal code: 1275002. ISSN: 0091-6749.

CY United States

DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199508

ED Entered STN: 19950911
Last Updated on STN: 19950911
Entered Medline: 19950830

AB Atopic dermatitis is characterized by elevated serum IgE concentrations and dysregulation of T-lymphocyte function. To examine the pattern of cytokine production associated with elevated IgE levels, phorbol ester plus ionomycin-stimulated production of interleukin (IL)-4, IL-5, and **interferon-gamma** (**IFN-gamma**) by blood mononuclear cells from 16 patients with atopic dermatitis was compared with that of 18 healthy subjects. Spontaneous in vitro IgE production was also studied longitudinally in patients receiving placebo or daily treatment with 0.05 mg/m2 **IFN-gamma**. Spontaneous in vitro IgE production and mitogen-driven IL-4 and **IFN-gamma** synthesis did not differ when patients were receiving **interferon** treatment compared with no treatment. Furthermore, ionomycin plus phorbol ester-stimulated mononuclear cells from patients with atopic dermatitis produced less IL-4 and more **IFN-gamma** than did cells from healthy subjects. IL-5 production by cells from patients with atopic dermatitis did not differ from that of cells from healthy subjects. The ratio of IL-4 to **IFN -gamma** produced in vitro was significantly lower ($p = 0.04$) in the cells of patients with atopic dermatitis (0.9) as compared with those of healthy subjects (2.7). The findings suggest that when circulating T

cells are stimulated under antigen presenting cell-independent conditions, atopic dermatitis is not characterized by the shift in the reciprocal relationship between IL-4 and **IFN-gamma** production, which has been postulated to explain the pathogenesis of IgE elevation and the therapeutic action of **IFN-gamma** in patients with atopic dermatitis.

CT Check Tags: Female; Human; Male; Support, U.S. Gov't, Non-P.H.S.
Adult
Antigen-Presenting Cells: PH, physiology
Cells, Cultured
*Cytokines: ME, metabolism
***Dermatitis, Atopic: DT, drug therapy**
***Dermatitis, Atopic: ME, metabolism**
Dose-Response Relationship, Drug
Double-Blind Method
*Immunoglobulin E: BI, biosynthesis
Interferon Type II: AD, administration & dosage
Interferon Type II: BI, biosynthesis
***Interferon Type II: TU, therapeutic use**
Interleukin-4: BI, biosynthesis
Interleukin-5: BI, biosynthesis
Middle Age
Mitogens: PD, pharmacology
Treatment Outcome

RN 207137-56-2 (Interleukin-4); 37341-29-0 (Immunoglobulin E); **82115-62-6 (Interferon Type II)**

CN 0 (Cytokines); 0 (Interleukin-5); 0 (Mitogens)

L73 ANSWER 14 OF 53 MEDLINE

AN 95323185 MEDLINE

DN 95323185 PubMed ID: 7599835

TI Cytokine interleukin-2, tumor necrosis factor-alpha, and **interferon-gamma** release after ischemia/reperfusion injury in a novel lung autograft animal model.

AU Serrick C; La Franchesca S; Giaid A; Shennib H

CS Joint Marseille Montreal Lung Transplant Program, Quebec, Canada.

SO AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, **(1995 Jul)** 152 (1) 277-82.
Journal code: 9421642. ISSN: 1073-449X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199508

ED Entered STN: 19950822
Last Updated on STN: 19950822
Entered Medline: 19950810

AB Previously, we have reported an increase in the cytokines interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-alpha), and **interferon-gamma** (**IFN-gamma**) early after left lung allotransplantation in dogs. The purpose of this study was to develop a novel model of canine lung autotransplantation and to observe whether ischemia/reperfusion injury alone (in the absence of an allogenic stimulus) would result in this cytokine release as seen in the allograft. Thus, using this model, early changes in cellular and cytokine composition in the lung autograft were monitored through the use of bronchoalveolar lavage (BAL) and plasma. The effects of ischemia/reperfusion injury on lung histology and major histocompatibility class II (MHC II) antigen expression were also observed. Ten mongrel dogs were subjected to left lung autotransplantation. Lungs were stored cold for 4 h, with a warm ischemic time of 1 h. BAL, blood, and biopsy specimens were taken preoperatively and 1 h, 4 h, 24 h, and 1 wk postoperatively. The mean BAL IL-2 levels significantly rose from a preoperative value of 150 +/- 19

pg/ml to 246 +/- 67 pg/ml 4 h after transplantation ($p < 0.05$), decreasing to preoperative levels after 24 h (128 +/- 54 pg/ml). Plasma levels of IL-2 did not change from preoperative values. In contrast to IL-2, TNF-alpha and **IFN-gamma** did not change in either BAL or plasma of the autograft.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Animal; Support, Non-U.S. Gov't
Bronchoalveolar Lavage Fluid: CH, chemistry
Bronchoalveolar Lavage Fluid: CY, cytology
Cell Count
Dogs
Enzyme-Linked Immunosorbent Assay
Histocompatibility Antigens Class II: AN, analysis
***Interferon Type II: ME, metabolism**
*Interleukin-2: ME, metabolism
*Lung: BS, blood supply
Lung: ME, metabolism
Lung: PA, pathology
*Lung Transplantation
Lung Transplantation: IM, immunology
Lung Transplantation: MT, methods
Lung Transplantation: PH, physiology
Reperfusion Injury: IM, immunology
***Reperfusion Injury: ME, metabolism**
Reperfusion Injury: PA, pathology
Transplantation, Autologous
*Tumor Necrosis Factor: ME, metabolism

RN **82115-62-6 (Interferon Type II)**

CN 0 (Histocompatibility Antigens Class II); 0 (Interleukin-2); 0 (Tumor Necrosis Factor)

L73 ANSWER 15 OF 53 MEDLINE

AN 95188223 MEDLINE

DN 95188223 PubMed ID: 7882381

TI Complete response of metastatic renal cell carcinoma to **low-dose interferon-gamma** treatment.

AU Otto F; Mackensen A; Mertelsmann R; Engelhardt R

CS Department of Medical Oncology, University Hospital Freiburg, Germany.

SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1995 Feb)** 40 (2) 115-8.
Journal code: 8605732. ISSN: 0340-7004.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199504

ED Entered STN: 19950425
Last Updated on STN: 19950425
Entered Medline: 19950412

AB The course of metastatic renal cell carcinoma may be positively influenced by immunotherapeutic agents. We report a case of renal cell carcinoma showing a complete response to once-weekly **low-dose** s.
c. **interferon-gamma (IFN gamma)**
treatment in multiple metastatic sites (lung, chest wall, abdomen, vertebral body), but concomitantly developing a solitary brain metastasis. High initial interleukin-6 (IL-6) levels returned to normal during **IFN** treatment suggesting that **IFN gamma** may have interrupted an autocrine IL-6/IL-6-receptor loop of the tumor cells. The duration of complete remission in the extracerebral sites is now 46+ months. **IFN gamma** may be less active beyond the blood/brain barrier.

CT Check Tags: Case Report; Human; Male; Support, Non-U.S. Gov't
C-Reactive Protein: ME, metabolism
***Carcinoma, Renal Cell: DT, drug therapy**
***Interferon Type II: AD, administration & dosage**

Interleukin-6: BL, blood
***Kidney Neoplasms: DT, drug therapy**
Middle Age
Neoplasm Metastasis
Platelet Count
Tomography, X-Ray Computed
RN **82115-62-6 (Interferon Type II)**; 9007-41-4 (C-Reactive Protein)
CN 0 (Interleukin-6)

L73 ANSWER 16 OF 53 MEDLINE
AN 95160140 MEDLINE
DN 95160140 PubMed ID: 7856752
TI Cytokine mRNA expression in postischemic/reperfused myocardium.
AU Herskowitz A; Choi S; Ansari A A; Wesselingh S
CS Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland.
NC P50-HL17655 (NHLBI)
SO AMERICAN JOURNAL OF PATHOLOGY, **(1995 Feb)** 146 (2) 419-28.
Journal code: 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950316
AB While the role of cytokines in mediating injury during hind limb skeletal muscle ischemia followed by reperfusion has recently been described, the role of cytokines in myocardial infarction and ischemia/reperfusion have remained relatively unexplored. We hypothesize that cytokines play an important role in the regulation of postischemic myocardial inflammation. This study reports the temporal sequence of proinflammatory cytokine gene expression in postischemic/reperfused myocardium and localizes interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha)-protein by immunostaining. Rats were subjected to either permanent left anterior descending (LAD) occlusion or to 35 minutes of LAD occlusion followed by reperfusion and sacrificed up to 7 days later. Rat-specific oligonucleotide probes were used to semiquantitatively assess the relative expression of mRNA for TNF-alpha, IL-1 beta, IL-2, IL-6, **interferon-gamma** (**IFN-gamma**), and transforming growth factor-beta 1 (TGF-beta 1) utilizing the reverse transcriptase-polymerase chain reaction amplification technique. Increased cardiac mRNA levels for all cytokines except IL-6 and **IFN-gamma** were measurable within 15 to 30 minutes of LAD occlusion and increased levels were generally sustained for 3 hours. During early reperfusion, mRNA levels for IL-6 and TGF-beta 1 were significantly reduced compared with permanent LAD occlusion. In both groups, cytokine mRNA levels all returned to baseline levels at 24 hours, while IL-1 beta, TNF-alpha, and TGF-beta 1 mRNA levels again rose significantly at 7 days only in animals with permanent LAD occlusion. Immunostaining for IL-1 beta and TNF-alpha protein revealed two patterns of reactivity: 1) microvascular staining for both IL-1 beta and TNF-alpha protein only in postischemic reperfused myocardium in early post-reperfusion time points; and 2) staining of infiltrating macrophages in healing infarct zones which was most prominent at 7 days after permanent LAD occlusion. These results provide evidence for local expression of cytokine mRNA in postischemic myocardium and suggest that regulation of local cytokine release is altered during the postischemic period.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Base Sequence
Disease Models, Animal

Immunohistochemistry
***Interferon Type II: ME, metabolism**
Interleukin-1: AN, analysis
Interleukin-1: ME, metabolism
*Interleukins: ME, metabolism
Molecular Sequence Data
*Myocardial Ischemia: ME, metabolism
Myocardial Ischemia: PA, pathology
***Myocardial Reperfusion Injury: ME, metabolism**
Myocardial Reperfusion Injury: PA, pathology
Myocardium: ME, metabolism
Myocardium: PA, pathology
Polymerase Chain Reaction
RNA, Messenger: ME, metabolism
Rats
Rats, Sprague-Dawley
Time Factors
*Transforming Growth Factor beta: ME, metabolism
Tumor Necrosis Factor: AN, analysis
*Tumor Necrosis Factor: ME, metabolism
RN **82115-62-6 (Interferon Type II)**
CN 0 (Interleukin-1); 0 (Interleukins); 0 (RNA, Messenger); 0 (Transforming Growth Factor beta); 0 (Tumor Necrosis Factor)

L73 ANSWER 17 OF 53 MEDLINE
AN 95153683 MEDLINE
DN 95153683 PubMed ID: 7850804
TI Treating tumor-bearing mice with **low-dose gamma-interferon** plus tumor necrosis factor alpha to diminish immune suppressive granulocyte-macrophage progenitor cells increases responsiveness to interleukin 2 immunotherapy.
AU Pak A S; Ip G; Wright M A; Young M R
CS Research Service, Department of Veterans Affairs, Hines VA Hospital, Illinois 60141.
NC CA-45080 (NCI)
CA-48080 (NCI)
SO CANCER RESEARCH, **(1995 Feb 15)** 55 (4) 885-90.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950314
AB Production of granulocyte-macrophage (GM) colony-stimulating factor by murine metastatic Lewis lung carcinoma cells (LLC-LN7) increases the number and distribution of GM progenitor cells that are suppressive to T cell responsiveness to interleukin 2 (IL-2). The presence of these GM suppressor cells can be diminished by treatment of LLC-LN7-bearing mice with **low doses** of 100 units **IFN-gamma** plus 10 units tumor necrosis factor alpha (TNF-alpha). The aim of this study was to determine whether treatment of LLC-LN7-bearing mice with **IFN-gamma**/TNF-alpha to diminish GM suppressor cell presence would increase the responsiveness to IL-2 immune stimulatory therapy (100-1000 IU, twice daily for 5 days). Treatment first with **IFN-gamma**/TNF-alpha and then also with **low dose** IL-2 increased both the numbers of CD4+ and CD8+ cells within the tumor and the levels of their expression of the p55 IL-2 receptor. These intratumoral T cells also had an increased cytolytic capacity toward autologous tumor cells and an increased capacity to proliferate and secrete IL-2. Such effects were observed to a lesser

extent in mice that were treated with either **IFN-gamma** /TNF-alpha alone or with **low doses** of IL-2 only. The combination treatment regimen of **IFN-gamma**/TNF-alpha and then IL-2 was also significantly more effective at reducing the size of the primary tumor and the formation of metastatic lung nodules than were the individual treatments. These results show that treatment to minimize the presence of GM suppressor cells enhances the effectiveness of IL-2 to stimulate anti-tumor immune responses and to diminish tumor growth and metastasis.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Antineoplastic Combined Chemotherapy Protocols: PD, pharmacology
Cell Division: DE, drug effects
Dose-Response Relationship, Drug
Drug Synergism
***Granulocytes: DE, drug effects**
***Granulocytes: IM, immunology**
*Immunotherapy
Interferon-gamma, Recombinant: AD, administration & dosage
***Interferon-gamma, Recombinant: PD, pharmacology**
Interleukin-2: AD, administration & dosage
*Interleukin-2: PD, pharmacology
***Lung Neoplasms: IM, immunology**
Lung Neoplasms: SC, secondary
***Lung Neoplasms: TH, therapy**
***Lymphocytes, Tumor-Infiltrating: DE, drug effects**
***Lymphocytes, Tumor-Infiltrating: IM, immunology**
***Macrophages: DE, drug effects**
***Macrophages: IM, immunology**
Mice
Mice, Inbred C57BL
***Stem Cells: DE, drug effects**
***Stem Cells: IM, immunology**
Stimulation, Chemical
T-Lymphocytes: DE, drug effects
T-Lymphocytes: IM, immunology
Tumor Necrosis Factor: AD, administration & dosage
*Tumor Necrosis Factor: PD, pharmacology

CN 0 (Antineoplastic Combined Chemotherapy Protocols); **0 (Interferon-gamma, Recombinant)**; 0 (Interleukin-2); 0 (Tumor Necrosis Factor)

L73 ANSWER 18 OF 53 MEDLINE
AN 95084476 MEDLINE
DN 95084476 PubMed ID: 7992355
TI The early release of interleukin-2, tumor necrosis factor-alpha and **interferon-gamma** after ischemia reperfusion injury in the lung allograft.
AU Serrick C; Adoumie R; Giaid A; Shennib H
CS Joint Marseille-Montreal Lung Transplant Program, Quebec, Canada.
SO TRANSPLANTATION, **(1994 Dec 15)** 58 (11) 1158-62.
Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199501
ED Entered STN: 19950124
Last Updated on STN: 19950124
Entered Medline: 19950106
AB A period of cold and warm ischemia is obligatory when performing lung transplantation. Subtle ischemia-reperfusion injury induced in the course of transplantation can pass undetected or cause a short phase of

reversible lung dysfunction. We hypothesized that ischemia-reperfusion injury may result in the local release of cytokines that have the capability to mediate acute lung injury early following transplantation. To test this hypothesis, 10 mongrel dogs were subjected to left lung allotransplantation. As performed in the clinical setting, donor lungs were preserved with Eurocollins solution and stored at 4 degrees C for 4 hr, which was followed by 1 hr of warm ischemia. Recipients received standard immunosuppression of cyclosporine, azathioprine, and low dose steroids. Bronchoalveolar lavage (BAL) and open lung biopsies were performed before operation and at approximately 1 hr, 4 hr, 24 hr, and 1 week after transplantation. A significant increase in BAL IL-2 levels was observed 4 hr after surgery (0 hr: 349 +/- 138 pg/ml; 4 hr: 757 +/- 284 pg/ml) (mean +/- SEM) ($P < 0.05$) which subsequently decreased 24 hr (320 +/- 168 pg/ml) after transplantation. BAL TNF-alpha levels were significantly increased 1 hr after transplantation ($P < 0.05$) (0 hr: 3.4 +/- 0.65 pg/ml; 1 hr: 13.3 +/- 8.0 pg/ml) returning to baseline after 24 hr (5.8 +/- 2.8 pg/ml). BAL **IFN-gamma** levels also significantly increased 1 and 4 hr after transplantation (0 hr: 7.2 +/- 2.1 pg/ml; 1 hr: 68.2 +/- 49.2 pg/ml; 4 hr: 301 +/- 131 pg/ml) ($P < 0.05$). This decreased back to baseline after 24 hr and 1 week (5.2 +/- 1.2 pg/ml and 9.7 +/- 7.9 pg/ml, respectively). There were no changes detected in plasma levels of cytokines. Histology showed evidence of grade 1-2 rejection after 1 week. We conclude that subjection of a lung allograft to standard periods of cold-warm ischemia will result in a temporary early elevation of IL-2, TNF-alpha, and **IFN-gamma** detectable only in the bronchoalveolar compartment. Such local increase in cytokines in the lung allograft may play an important role in the development of early allograft dysfunction.

CT Check Tags: Animal
Antibody Formation
Bronchoalveolar Lavage Fluid: CH, chemistry
Cell Differentiation
Cytokines: AN, analysis
Cytokines: BL, blood
Dogs
Immunity, Cellular
***Interferon Type II: ME, metabolism**
*Interleukin-2: ME, metabolism
Lung Transplantation: IM, immunology
*Lung Transplantation: PA, pathology
***Reperfusion Injury: ME, metabolism**
Time Factors
Transplantation, Homologous: IM, immunology
*Tumor Necrosis Factor: ME, metabolism

RN **82115-62-6 (Interferon Type II)**

CN 0 (Cytokines); 0 (Interleukin-2); 0 (Tumor Necrosis Factor)

L73 ANSWER 19 OF 53 MEDLINE

AN 95033518 MEDLINE

DN 95033518 PubMed ID: 7946588

TI **Low-dose gamma-interferon** therapy is ineffective in renal cell carcinoma patients with large tumour burden.

AU Aulitzky W E; Lerche J; Thews A; Luttichau I; Jacobi N; Herold M; Aulitzky W; Peschel C; Stockle M; Steinbach F; +

CS Department of Urology, General Hospital Salzburg, Austria.

SO EUROPEAN JOURNAL OF CANCER, **(1994)** 30A (7) 940-5.
Journal code: 9005373. ISSN: 0959-8049.

CY ENGLAND: United Kingdom

DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199412
ED Entered STN: 19950110
Last Updated on STN: 19990129
Entered Medline: 19941212
AB The efficacy and immunomodulatory effects of **low-dose gamma-interferon (gamma IFN)** were investigated in an unselected population of patients with metastasising renal cell carcinoma. 36 patients suffering from metastasising renal cell carcinoma with a performance status exceeding Karnofsky index of 50 were entered into the open phase I/II trial. The majority of the patients recruited displayed a large tumour burden, and 28 patients (78%) had metastases involving two to six organ sites. Treatment was started with a 2-week cycle of either daily or weekly subcutaneous administration of either 100, 200 or 400 micrograms **gamma IFN**. After a therapy-free interval of 2 weeks treatment was switched to the alternate mode of administration. Subsequently, treatment was continued with the same **dose** applied once a week for a minimum of 3 months. Serum levels of neopterin and beta-2-microglobulin, as well as flow cytometric analyses of peripheral blood mononuclear cells, were used for the assessment of biological response. Minimal antitumour activity was observed in this high-risk patient group and only 1 patient experienced a partial response (PR) lasting 36 + months. Comparison of the patients' characteristics to those of other **low-dose gamma IFN** trials revealed a highly significant difference in the tumour burden and clinical response. We conclude that patient selection is a decisive parameter for the outcome of treatment with **low-dose gamma IFN**, and that patients with poor prognostic features and a large tumour burden are not likely to respond to this almost atoxic treatment.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Carcinoma, Renal Cell: PA, pathology
***Carcinoma, Renal Cell: TH, therapy**
Dose-Response Relationship, Drug
Drug Administration Schedule
***Interferon Type II: AD, administration & dosage**
Interferon Type II: AE, adverse effects
Kidney Neoplasms: PA, pathology
***Kidney Neoplasms: TH, therapy**
Leukocyte Count
Leukopenia: ET, etiology
Middle Age
Neoplasm Metastasis
RN **82115-62-6 (Interferon Type II)**

L73 ANSWER 20 OF 53 MEDLINE
AN 94328354 MEDLINE
DN 94328354 PubMed ID: 8051732
TI Phase II trial of **low dose gamma-interferon** in metastatic renal cell carcinoma.
AU Ellerhorst J A; Kilbourn R G; Amato R J; Zukiwski A A; Jones E; Logothetis C J
CS Department of Genitourinary Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston 77030.
SO JOURNAL OF UROLOGY, **(1994 Sep)** 152 (3) 841-5.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals

EM 199409
ED Entered STN: 19940914
Last Updated on STN: 19940914
Entered Medline: 19940906
AB We conducted a phase II trial to confirm the activity of fixed, **low dose gamma-interferon** in metastatic renal cell carcinoma. A total of 35 patients with metastatic renal cell carcinoma, who had not received prior immunotherapy and who had a Zubrod performance status of 2 or less, was enrolled in this study. Primary tumors were controlled by nephrectomy or embolization before treatment began. **gamma-Interferon** was administered weekly as a subcutaneous injection at a fixed dose of 100 micrograms. Toxic effects were limited to low grade fever, chills and myalgias within 24 hours of injection. There were no incidences of grade 3 or 4 toxicity. Responses could be evaluated in 34 patients. There were 1 complete and 4 partial responses, for an objective response rate of 15% (95% confidence interval 5 to 32%). Durations of response to date are 21+, 17+, 13+, 9 and 2 months. We conclude that **gamma-interferon** is an active agent for metastatic renal cell carcinoma when administered according to this dose and schedule. The response rate compares favorably with those of alpha-**interferon** and interleukin-2, and toxicity is minimal. **gamma-Interferon** has excellent potential for use in combination with other biological or chemotherapeutic agents and in the adjuvant setting.
CT Check Tags: Female; Human; Male
Adult
Aged
Aged, 80 and over
***Carcinoma, Renal Cell: TH, therapy**
Injections, Subcutaneous
Interferon Type II: AD, administration & dosage
Interferon Type II: AE, adverse effects
***Interferon Type II: TU, therapeutic use**
***Kidney Neoplasms: TH, therapy**
Middle Age
Neoplasm Metastasis
RN **82115-62-6 (Interferon Type II)**

L73 ANSWER 21 OF 53 MEDLINE
AN 94130279 MEDLINE
DN 94130279 PubMed ID: 8299123
TI Increasing infiltration and activation of CD8+ tumor-infiltrating lymphocytes after eliminating immune suppressive granulocyte/macrophage progenitor cells with **low doses** of **interferon gamma** plus tumor necrosis factor alpha.
AU Young M R; McCloskey G; Wright M A; Pak A S
CS Research Service, Department of Veterans Affairs, Hines VA Hospital, IL 60141.
NC CA-45080 (NCI)
CA-48080 (NCI)
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1994 Jan)** 38 (1) 9-15.
Journal code: 8605732. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940318
Last Updated on STN: 19970203
Entered Medline: 19940308
AB By secreting granulocyte/macrophage colony-stimulating factor (GM-CSF), metastatic Lewis lung carcinoma (LLC-LN7) tumors induce the appearance of myelopoiesis-associated immune-suppressor cells that resemble

granulocytic-macrophage (GM) progenitor cells. The presence of these GM-suppressor cells in mice bearing LLC-LN7 tumors was associated with a reduced capacity of splenic T cells to proliferate in response to interleukin-2 (IL-2). Administration of **low doses** of 100 U **interferon gamma (IFN gamma)** plus 10 U tumor necrosis factor alpha (TNF alpha) to the tumor bearers, a combination treatment that we previously showed to diminish the presence of GM-suppressor cells synergistically, restored proliferative responsiveness of the splenic T cells to IL-2. These LLC-LN7-bearing mice were also examined for whether cells that phenotypically resemble GM-progenitor cells (ER-MP12+ cells) infiltrate the tumor mass. ER-MP12+ cells composed approximately 10% of the cells isolated from dissociated tumors of mice that had been treated with placebo or with either **IFN gamma** or TNF alpha alone, but **IFN gamma**/TNF alpha therapy markedly reduced the number of tumor-infiltrating ER-MP12+ suppressor cells. The **IFN gamma**/TNF alpha treatment to eliminate GM-suppressor cells and restore T cell responsiveness to IL-2 was next coupled with **low dose** IL-2 therapy (100 U twice daily). Addition of IL-2 to the treatment regimen did not significantly influence the effectiveness of the **IFN gamma**/TNF alpha treatment in eliminating GM-suppressor cells from the LLC-LN7 tumor mass. However, inclusion of IL-2 with the **IFN gamma**/TNF alpha treatment regimen enhanced the CD8+, but not the CD4+, cell content within the tumor, and diminished the number of metastatic lung nodules within the mice. When these tumors were excised, dissociated, and bulk-cultured with a **low dose** of IL-2, an increased level of cytotoxic T lymphocyte (CTL) activity was generated in the TIL cultures from mice that had received **IFN gamma**/TNF alpha plus IL-2 treatments. A lesser but detectable level of CTL activity was generated in TIL cultures from mice that were treated with only **IFN gamma** /TNF alpha, while no CTL activity was generated in tumor cultures from mice receiving only placebo or **low-dose** IL-2. These results suggest the effectiveness of **IFN gamma** plus TNF alpha therapy in restoring IL-2 responsiveness in mice bearing GM-suppressor cell-inducing tumors and at enhancing both the intratumoral CD8+ cell content and the generation of CTL activity in bulk cultures of these tumors.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

Antigens, CD8: BI, biosynthesis
Carcinoma: DT, drug therapy
***Carcinoma: IM, immunology**
Carcinoma: SC, secondary
Dose-Response Relationship, Drug
Granulocyte-Macrophage Colony-Stimulating Factor: PH, physiology
Granulocytes: DE, drug effects
Interferon Type II: AD, administration & dosage
***Interferon Type II: PD, pharmacology**
Interferon Type II: TU, therapeutic use
Interleukin-2: AD, administration & dosage
Interleukin-2: PD, pharmacology
Interleukin-2: TU, therapeutic use
Lung Neoplasms: DT, drug therapy
***Lung Neoplasms: IM, immunology**
Lung Neoplasms: SC, secondary
Lymphocyte Transformation
Lymphocytes, Tumor-Infiltrating: IM, immunology
***Lymphocytes, Tumor-Infiltrating: PH, physiology**
Macrophages: DE, drug effects
Mice
Mice, Inbred C57BL
T-Lymphocytes, Cytotoxic: DE, drug effects

***T-Lymphocytes, Suppressor-Effector: DE, drug effects**
Tumor Cells, Cultured
Tumor Necrosis Factor: AD, administration & dosage
*Tumor Necrosis Factor: PD, pharmacology
Tumor Necrosis Factor: TU, therapeutic use
RN **82115-62-6 (Interferon Type II)**; 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)
CN 0 (Antigens, CD8); 0 (Interleukin-2); 0 (Tumor Necrosis Factor)

L73 ANSWER 22 OF 53 MEDLINE
AN 94084662 MEDLINE
DN 94084662 PubMed ID: 8261414
TI 1 alpha,25-dihydroxyvitamin D3 plus **gamma-interferon** blocks lung tumor production of granulocyte-macrophage colony-stimulating factor and induction of immunosuppressor cells.
AU Young M R; Halpin J; Wang J; Wright M A; Matthews J; Pak A S
CS Department of Veterans Affairs, Hines VA Hospital 60141.
NC CA-45080 (NCI)
CA-48080 (NCI)
SO CANCER RESEARCH, **(1993 Dec 15)** 53 (24) 6006-10.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199401
ED Entered STN: 19940209
Last Updated on STN: 19940209
Entered Medline: 19940124
AB Metastatic Lewis lung carcinoma (LLC-LN7) cells have previously been shown to produce granulocyte-macrophage colony-stimulating factor (GM-CSF) which induces the appearance of immunosuppressive granulocytic-macrophage progenitor cells (GM-suppressor cells). The present in vitro studies showed that treatment of LLC-LN7 tumor cells with 1 alpha,25-dihydroxyvitamin D3 [1,25(OH)2D3] plus **low dose gamma-interferon (IFN-gamma)** resulted in a synergistic reduction in tumor GM-CSF secretion and a blockage in the capacity of the tumor cells to induce GM-suppressor cells. The production of GM-CSF by bulk cultures of enzymatically dissociated LLC-LN7 tumors that had been excised as s.c. tumors from mice was also blocked when the dissociated tumor was cultured with 1,25(OH)2D3 plus **IFN-gamma**. Our previous and present studies showed that GM-suppressor cells persist in bulk cultures of dissociated LLC-LN7 tumors after a 1-week period of culture. Addition of either 1,25(OH)2D3 or **IFN-gamma** did not diminish the persistence of GM-suppressor cells. However, when tumor production of GM-CSF was inhibited by culture with both 1,25(OH)2D3 and **IFN-gamma** , the ability of the dissociated tumor culture to sustain the presence of GM-suppressor cells was blocked. This elimination of GM-suppressor cells by treatment of the dissociated tumor with 1,25(OH)2D3 and **IFN-gamma** coincided with increased expansion of CD8+ tumor-infiltrating leukocytes and increased cytotoxic T-lymphocytes activity of tumor-infiltrating lymphocytes. These results suggest that blocking tumor production of GM-CSF can interrupt the suppressor-inducing cascade of the tumor and enhance expansion and anti-tumor cytolytic reactivity of tumor-infiltrating leukocytes.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Calcitriol: PD, pharmacology
Cells, Cultured
Cytotoxicity, Immunologic
*Granulocyte-Macrophage Colony-Stimulating Factor: BI, biosynthesis
***Interferon Type II: PD, pharmacology**

***Lung Neoplasms: ME, metabolism**
Mice
Mice, Inbred C57BL
***T-Lymphocytes, Suppressor-Effector: PH, physiology**
RN 32222-06-3 (Calcitriol); **82115-62-6 (Interferon Type II);**
83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)

L73 ANSWER 23 OF 53 MEDLINE
AN 93383344 MEDLINE
DN 93383344 PubMed ID: 8372410
TI [Results of **low dosage** cyclic **interferon-gamma** therapy of metastatic renal cell carcinoma]. Ergebnisse der niedrig dosierten zyklischen **Interferon-Gamma**-Therapie beim metastasierten Nierenzellkarzinom.
AU Hofmockel G; Wirth M P; Heimbach D; Frohmuller H G
CS Urologische Klinik und Poliklinik der Universitat Wurzburg.
SO UROLOGE. AUSGABE A, **(1993 Jul)** 32 (4) 290-4.
Journal code: 1304110. ISSN: 0340-2592.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 199310
ED Entered STN: 19931029
Last Updated on STN: 19931029
Entered Medline: 19931014
AB A total of 24 patients with metastatic renal cell carcinoma were treated with a **low-dose** cyclic regimen of **interferon-gamma (IFN-gamma)**. The **dosage** was 50 micrograms **IFN-gamma** s.c. per day for 5 days every 4 weeks. In 16 of the 24 patients nephrectomy had preceded this treatment. Another immunotherapy had already been performed in 13 of the 24 cases. No complete remission was achieved in any of the patients, all of whom were evaluable. One patient with pulmonary metastases achieved partial response. Stable disease lasting 2 to 12+ months was seen in 5 cases. Tumour progression was observed in 18 patients. Only slight side-effects were noted. Patient selection could be one reason for the wide range of response rates reported for **IFN-gamma** treatment in the literature.
CT Check Tags: Female; Human; Male
Adult
Aged
Aged, 80 and over
Carcinoma, Renal Cell: MO, mortality
Carcinoma, Renal Cell: PA, pathology
***Carcinoma, Renal Cell: TH, therapy**
Combined Modality Therapy
Drug Administration Schedule
English Abstract
Follow-Up Studies
Injections, Subcutaneous
***Interferon Type II: AD, administration & dosage**
Interferon-alpha: AD, administration & dosage
Interleukin-2: AD, administration & dosage
Kidney Neoplasms: MO, mortality
Kidney Neoplasms: PA, pathology
***Kidney Neoplasms: TH, therapy**
Middle Age
Neoplasm Metastasis
RN **82115-62-6 (Interferon Type II)**
CN 0 (Interferon-alpha); 0 (Interleukin-2)

L73 ANSWER 24 OF 53 MEDLINE

AN 93163841 MEDLINE
DN 93163841 PubMed ID: 1287141
TI **Gamma-interferon** enhances the cytotoxic activity of interleukin-2-induced peripheral blood lymphocyte (LAK) cells, tumor infiltrating lymphocytes (TIL), and effusion associated lymphocytes.
AU Papamichail M; Baxevanis C N
CS Department of Immunology, Hellenic Anticancer Institute, Athens, Greece.
SO JOURNAL OF CHEMOTHERAPY, **(1992 Dec)** 4 (6) 387-93.
Journal code: 8907348. ISSN: 1120-009X.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930402
Last Updated on STN: 19930402
Entered Medline: 19930316
AB The effect of **gamma-interferon** (**IFN-gamma**) on the induction of interleukin-2 (IL-2) activated killer cell activity was studied: (I) in peripheral blood lymphocytes (LAK cells) from cancer patients and healthy donors, (II) in lymphocytes infiltrating solid tumors (TIL) from melanoma and breast cancer patients, and (III) in pleural effusion associated lymphocytes (EAL) from patients with lung adenocarcinoma. The coculture of LAK, TIL and pleural effusion mononuclear cells (MNC) with several doses of **IFN-gamma** (10, 50, 250, and 1250 U/ml) and a **low dose** of IL-2 (10 U/ml) for 5 days resulted in a synergistic effect on the cytotoxicity of these cells against several tumor cell lines. Furthermore there was a potentiation in the proliferation of MNC after a 5-day culture. The induction of lymphocyte cytotoxicity by a combination of **IFN-gamma** with **low doses** of IL-2 may be helpful in designing more effective cancer immunotherapeutic protocols with LAK, TIL or EAL.
CT Check Tags: Human; Support, Non-U.S. Gov't
*Cytotoxicity, Immunologic: DE, drug effects
***Interferon Type II: TU, therapeutic use**
*Interleukin-2: TU, therapeutic use
Killer Cells, Lymphokine-Activated: IM, immunology
Lymphocyte Transformation
***Lymphocytes: IM, immunology**
Lymphocytes, Tumor-Infiltrating: IM, immunology
Neoplasms: IM, immunology
Neoplasms: TH, therapy
Pleural Effusion, Malignant: IM, immunology
RN **82115-62-6 (Interferon Type II)**
CN 0 (Interleukin-2)

L73 ANSWER 25 OF 53 MEDLINE
AN 92205422 MEDLINE
DN 92205422 PubMed ID: 1553580
TI Treatment of chronic myelogenous leukemia with different cytokines.
AU Wandl U B; Opalka B; Kloke O; Nagel-Hiemke M; Moritz T; Niederle N
CS Department of Internal Medicine, University of Essen, Germany.
SO SEMINARS IN ONCOLOGY, **(1992 Apr)** 19 (2 Suppl 4) 88-94.
Journal code: 0420432. ISSN: 0093-7754.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920509

Last Updated on STN: 19950206
Entered Medline: 19920430

AB In vitro data suggest a synergistic antiproliferative effect of different cytokines. In four clinical studies chronic myelogenous leukemia (CML) patients were treated with **interferon** (**IFN**)-alpha alone or **IFN**-alpha combined with either **low-dose IFN-gamma** or tumor necrosis factor (TNF)-alpha. The best response was achieved in previously untreated patients with good prognostic factors and highest tolerable **IFN** dose for maintenance treatment. Breakpoint localization within the major breakpoint cluster region did not correlate with response to **IFN**. In a randomized study of **IFN**-alpha versus **IFN**-alpha combined with **IFN-gamma**, no differences in response rates were observed. Patients with primary or secondary resistance to these treatment modalities received a combination therapy with **IFN**-alpha and TNF-alpha. In these patients, a decrease in leukocyte counts was noted, but no cytogenetic improvement occurred.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Blotting, Southern
Dose-Response Relationship, Drug
*Interferon-alpha: TU, therapeutic use
***Interferon-gamma, Recombinant: TU, therapeutic use**
Leukemia, Myeloid, Philadelphia-Positive: GE, genetics
***Leukemia, Myeloid, Philadelphia-Positive: TH, therapy**
Middle Age
*Tumor Necrosis Factor: TU, therapeutic use

CN 0 (Interferon-alpha); **0 (Interferon-gamma, Recombinant)**; 0 (Tumor Necrosis Factor)

L73 ANSWER 26 OF 53 MEDLINE
AN 91309086 MEDLINE
DN 91309086 PubMed ID: 1906780
TI Enhancement of metastatic potential by **gamma-interferon**.
AU Kelly S A; Gschmeissner S; East N; Balkwill F R
CS Biological Therapy Laboratory, Imperial Cancer Research Fund, London, England.
SO CANCER RESEARCH, **(1991 Aug 1)** 51 (15) 4020-7.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199108
ED Entered STN: 19910913
Last Updated on STN: 19970203
Entered Medline: 19910828

AB Preincubation of murine colon 26 colon adenocarcinoma cells with **gamma-interferon** (**IFN-gamma**), but not alpha-**interferon**, produced a significant increase in experimental pulmonary metastases in syngeneic BALB/c and T-cell-deficient BALB/c nude mice. The enhancement was seen after as little as 1 h of exposure to 1 unit/ml of **IFN-gamma** and persisted for at least 72 h following removal of the cytokine. **IFN-gamma** exerted its effects by increasing the pulmonary retention of cells during the first 6 h following tumor cell injection. During this period all cells visualized in the lung were trapped in pulmonary capillaries. The enhancement was not due to modulations in class I major histocompatibility complex surface antigen expression; nor was it due to alterations in cell size, adhesion to components of the extracellular matrix in vitro, heterotypic or homotypic adhesion, sensitivity to lysis

by activated peritoneal macrophages, osmotic fragility, enhancement of surface class II major histocompatibility complex antigen expression, or enhancement of intercellular adhesion molecule-1 (ICAM-1). Colon 26 was completely resistant to natural killer cell-mediated lysis in vitro, and **IFN-gamma** did not modulate the ability of colon 26 to form conjugates with isolated splenocytes. In vivo elimination of anti-asialo GM1 + cells increased pulmonary metastasis, and in such mice, there was no longer a difference in metastatic potential between control and **IFN-gamma**-treated cells. We conclude that **low doses** of **IFN-gamma** generated at the site of the tumor by host-infiltrating cells or during cytokine therapy could enhance the survival of tumor cells in the circulation and enhance their metastatic potential.

CT Check Tags: Animal; Female
Adenocarcinoma: GE, genetics
Adenocarcinoma: IM, immunology
Adenocarcinoma: PA, pathology
Antibodies: PD, pharmacology
Cell Adhesion: DE, drug effects
Cell Division: DE, drug effects
Colonic Neoplasms: GE, genetics
Colonic Neoplasms: IM, immunology
Colonic Neoplasms: PA, pathology
Extracellular Matrix: DE, drug effects
Extracellular Matrix: ME, metabolism
Gene Expression: DE, drug effects
Glycosphingolipids: IM, immunology
Histocompatibility Antigens Class I: PH, physiology
Idoxuridine: ME, metabolism
***Interferon Type II: PD, pharmacology**
Iodine Radioisotopes: DU, diagnostic use
Killer Cells, Natural: IM, immunology
Lung Neoplasms: PA, pathology
Lung Neoplasms: SC, secondary
Lung Neoplasms: UL, ultrastructure
Macrophages: IM, immunology
Mice
Mice, Inbred BALB C
Mice, Nude
***Neoplasm Metastasis: PA, pathology**
Oncogenes: DE, drug effects
Tumor Cells, Cultured

RN 54-42-2 (Idoxuridine); 71012-19-6 (asialo GM1 ganglioside); **82115-62-6 (Interferon Type II)**

CN 0 (Antibodies); 0 (Glycosphingolipids); 0 (Histocompatibility Antigens Class I); 0 (Iodine Radioisotopes)

L73 ANSWER 27 OF 53 MEDLINE
AN 91277884 MEDLINE
DN 91277884 PubMed ID: 1905348
TI **Low-dose interferon gamma** renders neuroblastoma more susceptible to interleukin-2 immunotherapy.
AU Sigal R K; Lieberman M D; Reynolds J V; Shou J; Ziegler M M; Daly J M
CS Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia.
NC 5-T32-CA 09619-0 (NCI)
SO JOURNAL OF PEDIATRIC SURGERY, **(1991 Apr)** 26 (4) 389-95; discussion 395-6.
Journal code: 0052631. ISSN: 0022-3468.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199107
ED Entered STN: 19910818
Last Updated on STN: 19910818
Entered Medline: 19910731
AB Neuroblastoma remains a common and deadly childhood tumor, resistant to both surgical and chemo/radiotherapeutic intervention in its advanced stages. The role of immunotherapy in such cancers has yet to be defined. In previous work, we found that the addition of **interferon gamma** (**IFN-gamma**) to 3-day in vitro tissue cultures of the murine neuroblastoma C1300, led not only to the tumor's increased cell surface expression of the immunologically important major histocompatibility complex (MHC) class I antigen, but also to an increased susceptibility of such modified tumor to subsequent lymphokine activated killer (LAK) cell lysis. In this study, we sought to determine the in vivo applicability of these findings. Initial **dose**-response studies helped define a regimen of rIFN-**gamma**'s administration that upregulated MHC class I without activating host natural killer (NK) activity. A/J mice bearing 7-day-old subcutaneous C1300 were randomized to receive daily morning injections of either 0, 25,000, 50,000, or 100,000 U of rIFN-**gamma** intraperitoneally for 6 days. Animals were killed at days 3, 6, and 9 after initiation of rIFN-**gamma** therapy, and tumors were excised, digested, and stained for both MHC class I and II expression. At the time of sacrifice, splenocytes from each animal were tested for NK cytotoxicity toward YAC (an NK-sensitive lymphoma) and C1300. These studies defined 3 days of therapy with 25,000 U as a "priming" **dose** that increased expression of class I with minimal impact on NK activity.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Analysis of Variance
Cytotoxicity, Immunologic
Dose-Response Relationship, Drug
Immunotherapy
***Interferon Type II: AD, administration & dosage**
*Interleukin-2: TU, therapeutic use
Mice
Mice, Inbred A
***Neuroblastoma: TH, therapy**
Survival Rate
RN **82115-62-6 (Interferon Type II)**
CN 0 (Interleukin-2)

L73 ANSWER 28 OF 53 MEDLINE
AN 91264821 MEDLINE
DN 91264821 PubMed ID: 1646605
TI Signal transduction pathways in the induction of HLA class I antigen expression on Huh 6 cells by **interferon-gamma**.
AU Towata T; Hayashi N; Katayama K; Takehara T; Sasaki Y; Kasahara A; Fusamoto H; Kamada T
CS First Department of Medicine, Osaka University Medical School, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1991 Jun 14)** 177 (2) 610-8.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199107
ED Entered STN: 19910802
Last Updated on STN: 19970203
Entered Medline: 19910712
AB This study investigated the intracellular signal transduction regulating the appearance of HLA class I antigens on Huh 6 cells induced by

interferon-gamma. The expression was blocked by a protein kinase C inhibitor, H-7, but not by a calmodulin antagonist, W-7, nor by a protein kinase A inhibitor, H-8, at **low dose**. The antigen expression was induced by a direct activator of protein kinase C, phorbol myristate acetate, but not by calcium ionophore A23187 nor an analog of cAMP, dbcAMP. Therefore, we concluded that protein kinase C is involved in the expression of HLA class I antigens on Huh 6 cells induced by **interferon-gamma** but Ca(2+)-calmodulin and cAMP are not.

CT Check Tags: Human
1-(5-Isoquinolinesulfonyl)-2-methylpiperazine
Calcimycin: PD, pharmacology
Calmodulin: PD, pharmacology
***Carcinoma, Hepatocellular: IM, immunology**
Cell Line
Cyclic CMP: AA, analogs & derivatives
Cyclic CMP: PD, pharmacology
*Histocompatibility Antigens Class I: BI, biosynthesis
***Interferon Type II: PD, pharmacology**
Isoquinolines: PD, pharmacology
***Liver Neoplasms: IM, immunology**
Piperazines: PD, pharmacology
Signal Transduction: DE, drug effects
*Signal Transduction: IM, immunology
Sulfonamides: PD, pharmacology
Tetradecanoylphorbol Acetate: PD, pharmacology
Tumor Cells, Cultured

RN 16561-29-8 (Tetradecanoylphorbol Acetate); 3616-08-8 (Cyclic CMP); 52665-69-7 (Calcimycin); 64649-87-2 (dibutyryl cyclic-3',5'-cytidine monophosphate); 65595-90-6 (W 7); **82115-62-6 (Interferon Type II)**; 84477-87-2 (1-(5-Isoquinolinesulfonyl)-2-methylpiperazine); 84478-11-5 (N-(2-(methylamino)ethyl)-5-isoquinolinesulfonamide)

CN 0 (Calmodulin); 0 (Histocompatibility Antigens Class I); 0 (Isoquinolines); 0 (Piperazines); 0 (Sulfonamides)

L73 ANSWER 29 OF 53 MEDLINE
AN 91138670 MEDLINE
DN 91138670 PubMed ID: 1899831
TI Ciprofloxacin inhibits human hematopoietic cell growth: synergism with tumor necrosis factor and interferon.
AU Hahn T; Barak Y; Liebovich E; Malach L; Dagan O; Rubinstein E
CS Pediatric Research Institute, Kaplan Hospital, Rehovot, Israel.
SO EXPERIMENTAL HEMATOLOGY, **(1991 Mar)** 19 (3) 157-60.
Journal code: 0402313. ISSN: 0301-472X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199103
ED Entered STN: 19910412
Last Updated on STN: 19910412
Entered Medline: 19910326

AB The cytokines tumor necrosis factor (TNF) and **interferon** (**IFN**) induce antiproliferative and cytotoxic activity in a variety of cell types. Ciprofloxacin (CFN)--a new fluoroquinolone antibiotic--has also been described, at high concentrations, to suppress hematopoietic cell growth and to affect cytokine production. This study examines the possible relationship between TNF alpha and **IFN gamma**, as components of host defense mechanisms, and CFN. To investigate the effect of CFN, either alone or combined with TNF or **IFN**, on normal human hematopoiesis, we examined in vitro changes in hematopoietic progenitor cell growth. We also studied the effect of CFN on human cytokine production by determining TNF, **IFN**, and

colony-stimulating factor (CSF) production by human mononuclear leukocytes (MNC). Granulocyte and **monocyte** colony formation (granulocyte-macrophage colony-forming cells, GM-CFC) as well as erythroid burst formation (erythroid burst-forming units, BFU-E) were inhibited only by high nontherapeutic levels of CFN. Lower CFN concentrations, however, were inhibitory in the presence of low, noninhibitory concentrations of human recombinant (r)**IFN gamma** or rTNF alpha. CFN induced a striking dose-dependent increase in **IFN gamma** production and a decrease in CSF production by mitogen-stimulated MNC. No effect was observed, however, on TNF production by stimulated MNC. The synergistic inhibition of hematopoietic progenitor cell proliferation, achieved by combining **low doses** of CFN and of antiproliferative cytokines, may explain the occasional case of leukopenia or anemia observed in infected patients receiving CFN. This effect may also indicate the applicability of such a combination against malignant cell growth.

CT Check Tags: Human
Cell Division: DE, drug effects
Cerebrospinal Fluid: ME, metabolism
*Ciprofloxacin: PD, pharmacology
Cytokines: ME, metabolism
Dose-Response Relationship, Drug
Drug Synergism
Erythrocytes: DE, drug effects
Granulocytes: DE, drug effects
*Hematopoiesis: DE, drug effects
Interferon Type II: ME, metabolism
***Interferon Type II: PD, pharmacology**
Leukocytes, Mononuclear: ME, metabolism
Macrophages: DE, drug effects
Recombinant Proteins: PD, pharmacology
Tumor Necrosis Factor: ME, metabolism
*Tumor Necrosis Factor: PD, pharmacology

RN **82115-62-6 (Interferon Type II)**; 85721-33-1 (Ciprofloxacin)

CN 0 (Cytokines); 0 (Recombinant Proteins); 0 (Tumor Necrosis Factor)

L73 ANSWER 30 OF 53 MEDLINE

AN 91055377 MEDLINE

DN 91055377 PubMed ID: 2122928

TI Phase I trial with recombinant interleukin-2 (rIL-2): immune activation by rIL-2 alone or following pretreatment with recombinant **interferon -gamma**.

AU Farace F; Mathiot C; Brandely M; Tursz T; Dorval T; Pouillart P; Triebel F; Hercend T; Fridman W H

CS Institut Gustave Roussy, Villejuif, France.

SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, **(1990 Nov)** 82 (2) 194-9. Journal code: 0057202. ISSN: 0009-9104.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199012

ED Entered STN: 19910222
Last Updated on STN: 19910222
Entered Medline: 19901231

AB Alterations of immunological parameters were analysed in patients with advanced malignancies during a phase I trial with rIL-2. Five-day infusions of rIL-2 at doses from 1 x 10(6) to 24 x 10(6) biological response modifiers program (BRMP) U/m2 per day were given to 29 patients, with a minimum of three patients per dose. The dose of 24 x 10(6) U/m2 per day was the maximal tolerated dose (MTD). Immunological parameters were analyzed at days 0, 8 and 11 of the rIL-2 courses. Following a leucopenia during rIL-2 infusion, a lymphocytosis was found in all patients except

one. The lymphocytosis peaked at day 8 and was detected at doses of rIL-2 as low as 1 x 10(6) U/m2 per day, reaching a plateau at a dose of 16 x 10(6) U/m2 per day. Although all lymphocyte subsets were increased in patients receiving rIL-2, some patients had predominant T cells (CD3+, NKH1(CD56)-), others had predominant natural killer (NK) cells (CD3-, NKH1 (CD56)+), and yet others showed a mixed profile. A strong induction of cells cytotoxic for K562 targets was found in all patients at days 8 and 11. Eighteen patients received, 1 month later, a second treatment in which infusion of rIL-2 was preceded by a course of 5 days infusion of 2 x 10(6) U/m2 per day recombinant **interferon-gamma** (rIFN-**gamma**). The infusion of rIFN-**gamma** prior to rIL-2 had no effect on the rIL-2-induced alterations of immunological parameters. Taken together, our results suggest that immune stimulation by rIL-2 occurs even at **low doses** and is maximal at a dose below the MTD; and that pretreatment with **low-dose** rIFN-**gamma** does not modify the immune stimulation by rIL-2.

CT Check Tags: Human; Support, Non-U.S. Gov't
Cytotoxicity, Immunologic
Dose-Response Relationship, Drug
Drug Evaluation
Drug Therapy, Combination
***Interferon-gamma, Recombinant: TU, therapeutic use**
Interleukin-2: AD, administration & dosage
*Interleukin-2: TU, therapeutic use
Leukocyte Count
Lymphocyte Subsets
Lymphocytes: IM, immunology
Neoplasms: IM, immunology
***Neoplasms: TH, therapy**
Recombinant Proteins: AD, administration & dosage
Recombinant Proteins: TU, therapeutic use

CN **0 (Interferon-gamma, Recombinant)**; 0 (Interleukin-2); 0 (Recombinant Proteins)

L73 ANSWER 31 OF 53 MEDLINE
AN 90346454 MEDLINE
DN 90346454 PubMed ID: 2143498
TI Myelopoiesis-associated suppressor-cell activity in mice with Lewis lung carcinoma tumors: **interferon-gamma** plus tumor necrosis factor-alpha synergistically reduce suppressor cell activity.
AU Young M R; Young M E; Wright M A
CS Department of Research Services, Hines V.A. Hospital, IL 60141.
SO INTERNATIONAL JOURNAL OF CANCER, **(1990 Aug 15)** 46 (2) 245-50. Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199009
ED Entered STN: 19901026
Last Updated on STN: 19901026
Entered Medline: 19900917
AB The myelopoietic stimulation which occurs in mice bearing metastatic Lewis lung carcinoma (LLC-C3) tumors is accompanied by immune suppression and the appearance of myelopoiesis-associated immune suppressor cells in the bone marrow and spleen. **Low doses** of recombinant murine **interferon-gamma** (**IFN-gamma**) plus recombinant human tumor necrosis factor-alpha (TNF-alpha) were used to limit myelopoiesis and, in turn, reduce the presence of myelopoiesis-associated immune suppressor cells in LLC-C3 tumor bearers. Neither **IFN-gamma** nor TNF-alpha alone had any effect in vitro on the growth of myeloid progenitor cells into colonies or on the suppressive activity of bone-marrow cells from LLC-C3-bearing mice.

However, the combination of **low doses** of **IFN -gamma** and TNF-alpha synergistically inhibited both the growth of myeloid progenitor cells into colonies and the suppressive activity of bone-marrow cells from tumor-bearers. Similar results were obtained in vivo. When used alone, neither **IFN-gamma** nor TNF-alpha had any effect on myelopoiesis or on suppressor-cell activity. When combined, **IFN-gamma** plus TNF-alpha synergistically suppressed myelopoiesis and the presence of immune suppressive cells both in the bone marrow and in the spleen of tumor bearers. T-lymphocyte blastogenic and NK cytotoxic activities of the tumor-bearers were restored only after treatment with both **IFN-gamma** and TNF-alpha.

CT Check Tags: Animal; Comparative Study; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Bone Marrow: DE, drug effects
*Bone Marrow: IM, immunology
Colony-Forming Units Assay
Depression, Chemical
Dose-Response Relationship, Drug
Drug Synergism
Hematopoiesis: DE, drug effects
*Hematopoiesis: IM, immunology
Immune Tolerance: DE, drug effects
Immune Tolerance: IM, immunology
***Interferon-gamma, Recombinant: TU, therapeutic use**
***Lung Neoplasms: IM, immunology**
Lung Neoplasms: TH, therapy
Mice
Mice, Inbred C57BL
Recombinant Proteins: TU, therapeutic use
T-Lymphocytes, Suppressor-Effector: DE, drug effects
***T-Lymphocytes, Suppressor-Effector: IM, immunology**
*Tumor Necrosis Factor: TU, therapeutic use

CN **0 (Interferon-gamma, Recombinant)**; 0 (Recombinant Proteins); 0 (Tumor Necrosis Factor)

L73 ANSWER 32 OF 53 MEDLINE
AN 90275302 MEDLINE
DN 90275302 PubMed ID: 2112414
TI Sensitivity of chronic myeloid leukemia hemopoietic progenitors to PTT-119 in combination with human recombinant **interferon** alpha and **gamma**.
AU Visani G; Lemoli R M; Tosi P; Verlicchi F; Gamberi B; Cenacchi A R; Colombini R; Fogli M; Russo D; Zuffa E; +
CS Istituto di Ematologia L. e A. Seragnoli, Universita di Bologna, Italy.
SO BLUT, **(1990 May)** 60 (5) 287-90.
Journal code: 0173401. ISSN: 0006-5242.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199007
ED Entered STN: 19900824
Last Updated on STN: 20000303
Entered Medline: 19900713
AB PTT-119, a new synthetic alkylating compound, has shown a marked "in vitro" inhibitory effect on chronic myeloid leukemia (CML) granulo-**monocytic** precursors (CFU-GM) at doses greater than 5 micrograms/ml. Based on previous experiences of synergistic associations between alkylating drugs and biological modifiers, we tested the effects of **low doses** of PTT-119 (from 0.1 to 1 microgram/ml) in concert with alpha, **gamma**, or alpha + **gamma** **interferons** and compared to **IFNs** alone, in order to

investigate an alternative choice for treatment of CML patients in chronic phase. Our results showed a significantly higher CFU-GM cloning inhibition after addition of 100 or 1,000 U/ml of alpha **IFN** to 0.1 microgram/ml PTT-119 (from 39.6% +/- 26.6 SD to 80.7% +/- 10 SD and 91.5% +/- 8 SD, respectively), while **gamma IFN** resulted in only a slight increase in colony growth inhibition when compared to the drug used alone. The association of alpha plus **gamma IFN** coupled with PTT-119 treatment did not significantly improve the results observed after exposure of leukemic progenitors to PTT-119 and alpha **IFN** alone. We conclude that a combined treatment with PTT-119 and **IFN** is probably worth testing both for purging methods before autologous bone marrow transplantation and for in vivo administration in chronic myeloid leukemia.

CT Check Tags: Human; Support, Non-U.S. Gov't
*Antineoplastic Agents: PD, pharmacology
Dose-Response Relationship, Drug
Drug Therapy, Combination
***Hematopoietic Stem Cells: DE, drug effects**
*Interferon Type I, Recombinant: PD, pharmacology
***Interferon-gamma, Recombinant: PD, pharmacology**
***Leukemia, Myeloid, Chronic: BL, blood**
Leukemia, Myeloid, Philadelphia-Positive: BL, blood
*Nitrogen Mustard Compounds: PD, pharmacology
RN 83996-50-3 (ambamustine)
CN 0 (Antineoplastic Agents); 0 (Interferon Type I, Recombinant); 0 **(Interferon-gamma, Recombinant)**; 0 (Nitrogen Mustard Compounds)

L73 ANSWER 33 OF 53 MEDLINE
AN 90257644 MEDLINE
DN 90257644 PubMed ID: 2160521
TI Phase I studies of recombinant **interferon-gamma**.
AU Laszlo J; Goldstein D; Gockerman J; Hood L; Huang A T; Triozzi P; Sedwick W D; Koren H; Ellinwood E H; Tso C Y
CS American Cancer Society, Atlanta, GA 30329.
NC NOI-CM-07436 (NCI)
SO JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, **(1990 Apr)** 9 (2) 185-93.
Journal code: 8219656. ISSN: 0732-6580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199006
ED Entered STN: 19900720
Last Updated on STN: 19900720
Entered Medline: 19900627
AB A phase I study of the effects of intravenous administration of **interferon-gamma** on 31 patients was performed. The effects of dose, schedule, and chronic administration were studied. In the first phase of the study, a dose range of 0.01-500 MU/m2 (0.0002-25 mg/m2) was tested and we found the maximum tolerated dose to be 400 MU/m2; the dose-limiting toxicity with this preparation was hypotension. In the second phase, three different schedules of administration were tested. There were no significant differences in toxicity between a 20 min, a 4 h, or a 24 h infusion of 60 MU/m2 (3 mg/m2). In the third phase, patients received chronic administration of either 1 or 30 MU/m2. Patients given 30 MU/m2 twice a week for 4 weeks showed more symptoms--fever, nausea, and orthostasis--than those treated with 1 MU/m2. No significant changes were seen in natural killer cell activity, antibody-dependent complement cytotoxicity, or **monocyte** cytotoxicity at any dose. Maximal stimulation of 2',5'-oligodenylate synthetase occurred at **low doses** (12 MU/m2). Depressed bone marrow colony formation for CFU-GM, BFU-E, and CFU-GEMM in vivo was noted. No objective antitumor

responses were noted. This preparation of recombinant **interferon -gamma** can be given in doses as high as 400 MU/m2. Chronic administration would appear to be limited to 30 MU/m2. However, lower doses may give maximal biologic responses. These studies provide further information on the biologic effects of a wide dose range and a variety of schedules of recombinant **interferon-gamma**.

CT Check Tags: Female; Human; Male; Support, U.S. Gov't, P.H.S.
2',5'-Oligoadenylate Synthetase: ME, metabolism
Adult
Aged
Antibody-Dependent Cell Cytotoxicity: IM, immunology
Bone Marrow Cells
Colony-Forming Units Assay
Corticotropin: BL, blood
Cytotoxicity, Immunologic
Dose-Response Relationship, Drug
Drug Evaluation
Hydrocortisone: BL, blood
Interferon-gamma, Recombinant: AD, administration & dosage
***Interferon-gamma, Recombinant: AE, adverse effects**
Interferon-gamma, Recombinant: PD, pharmacology
Killer Cells, Natural: IM, immunology
Middle Age
Monocytes: IM, immunology
Neoplasms: BL, blood
Neoplasms: IM, immunology
Neoplasms: PA, pathology

RN 50-23-7 (Hydrocortisone); 9002-60-2 (Corticotropin)

CN **0 (Interferon-gamma, Recombinant)**; EC 2.7.7.- (2',5'-Oligoadenylate Synthetase)

L73 ANSWER 34 OF 53 MEDLINE

AN 90187301 MEDLINE

DN 90187301 PubMed ID: 2107219

TI The effect of intralesional **interferon gamma** on basal cell carcinomas.

AU Edwards L; Whiting D; Rogers D; Luck K; Smiles K A

CS Department of Internal Medicine (Dermatology), University of Arizona Medical Center, Tucson.

SO JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, **(1990 Mar)** 22 (3) 496-500.
Journal code: 7907132. ISSN: 0190-9622.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199004

ED Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900418

AB This open label study evaluated the effect of nine intralesional injections of two different doses of **interferon gamma** on basal cell carcinomas in 29 patients. One group of 15 patients received **interferon gamma**, 0.01 mg (20,000 IU), intralesionally three times a week for 3 weeks. Fourteen patients received **interferon gamma**, 0.05 mg (100,000 IU), intralesionally in the same dosage schedule. Excisional biopsy specimens 12 weeks after therapy showed no evidence of tumor remaining in 7 of 14 patients (50%) treated with the higher dose of **interferon gamma**, whereas only 1 of 15 patients (7%) treated with **low-dose interferon gamma** was cured according to histologic criteria ($p = 0.025$). Seventy-six percent of patients reported at least one adverse reaction, but most were considered mild by the patient and the

investigator.
CT Check Tags: Human
Adult
Aged
Biopsy
Carcinoma, Basal Cell: PA, pathology
***Carcinoma, Basal Cell: TH, therapy**
Double-Blind Method
Drug Administration Schedule
Injections, Intralesional
Interferon Type II: AD, administration & dosage
***Interferon Type II: TU, therapeutic use**
Middle Age
Random Allocation
Skin Neoplasms: PA, pathology
***Skin Neoplasms: TH, therapy**
RN **82115-62-6 (Interferon Type II)**

L73 ANSWER 35 OF 53 MEDLINE
AN 89162993 MEDLINE
DN 89162993 PubMed ID: 2976544
TI Antiproliferative effect of Hu-**interferon-gamma** in 674V and J82 bladder carcinoma cell lines.
AU Jakse G; Marth C; Zechner J; Daxenbichler G
CS Urological Clinic and Policlinic, Technical University, Munich, Federal Republic of Germany.
SO UROLOGICAL RESEARCH, **(1988)** 16 (6) 403-5.
Journal code: 0364311. ISSN: 0300-5623.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198904
ED Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890418
AB Hu-**IFN-gamma** was evaluated in regard to the antiproliferative effect on J82 and 647V bladder cancer cell lines. In addition, the **IFN**-receptors were determined. There was a significant growth inhibition of J82 as well as 647V at **low dose** Hu-**IFN**-g (1 U/ml). The growth inhibition was significantly higher in 647V than in J82. The binding assay for 125J-Hu-**IFN**-g revealed 870 and 3,000 binding sites for 647V and J82, respectively, indicating that the antiproliferative effect of Hu-**IFN**-g may not depend on the absolute amount of **IFN** -receptors, in the two cell lines tested.
CT Check Tags: Human
***Bladder Neoplasms: PA, pathology**
***Carcinoma: PA, pathology**
Cell Division: DE, drug effects
***Interferon Type II: PD, pharmacology**
Receptors, Immunologic: PH, physiology
Receptors, Interferon
***Tumor Cells, Cultured: PA, pathology**
RN **82115-62-6 (Interferon Type II)**
CN 0 (Receptors, Immunologic); 0 (Receptors, Interferon)

L73 ANSWER 36 OF 53 MEDLINE
AN 89040969 MEDLINE
DN 89040969 PubMed ID: 3141856
TI [Treatment of metastatic kidney cancer with recombinant alpha-2 or **gamma interferon**. Results of 2 clinical phase II and III studies].

Die Behandlung des metastasierenden Nierenkarzinoms mit rekombinantem alpha-2- oder **gamma-Interferon**. Ergebnisses zweier klinischer Phase-II- bzw. -III-Studien.

AU Otto U; Schneider A; Denkhaus H; Conrad S
CS Urologische Universitatsklinik, Hamburg.

SO ONKOLOGIE, **(1988 Aug)** 11 (4) 185-91.
Journal code: 7808556. ISSN: 0378-584X.
CY Switzerland
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 198812
ED Entered STN: 19900308
Last Updated on STN: 20000303
Entered Medline: 19881215

AB In a phase-II and a phase-III study patients with histopathologically documented metastatic renal cell carcinoma were treated either with **gamma-interferon** in two different doses (100 micrograms/m2 3x/week for 4 h i.v. every other week or 500 micrograms/m2 5x/week for 24 h i.v. every other week) or with alpha-2-**interferon** alone (18 x 10(6) U 3x/week weekly i.m.) or in combination with vinblastine (0.1 mg/kg every third week i.v.). The purpose of these studies was to evaluate the response rate, the duration of response, the survival, the efficacy and the toxicity of the different forms of treatment. The overall response rate to **gamma-interferon** was 30% in both regimens. The response rate of treatment with alpha-2-**interferon** was found to be 31%. The duration of response ranged between 2 and 34+ months in patients treated with **gamma-interferon** and between 2 and 24+ months in those receiving alpha-2-**interferon**. Patients with objective tumor response showed a significantly longer survival than those not responding (p = 0.0056). **Low-dose-gamma-interferon** and alpha-2-**interferon** treatment could be easily done on an outpatient basis. In conclusion, **interferon** treatment seems to be of value in the therapy of patients with well documented progressive disease in metastatic renal cell cancer.

CT Check Tags: Comparative Study; Female; Human; Male
Adult
Aged
***Carcinoma, Renal Cell: TH, therapy**
Clinical Trials
Combined Modality Therapy
Dose-Response Relationship, Drug
Drug Administration Schedule
Drug Evaluation
English Abstract
*Interferon Alfa-2a: TU, therapeutic use
*Interferon Type I, Recombinant: TU, therapeutic use
***Interferon-gamma, Recombinant: TU, therapeutic use**
***Kidney Neoplasms: TH, therapy**
Middle Age
Neoplasm Metastasis
Vinblastine: TU, therapeutic use
RN 76543-88-9 (Interferon Alfa-2a); 865-21-4 (Vinblastine)
CN 0 (Interferon Type I, Recombinant); **0 (Interferon-gamma, Recombinant)**

L73 ANSWER 37 OF 53 MEDLINE
AN 88199060 MEDLINE
DN 88199060 PubMed ID: 2834451
TI Effects of vitamin D3 and **IFN-gamma** on the synthesis

of the second complement component, C2, by a human myeloid leukemia (HL-60) cell line.
AU Littman B H; Sanders K M
CS Medical Service, McGuire Veterans Administration Medical Center, Richmond, VA 23249.
SO JOURNAL OF IMMUNOLOGY, **(1988 May 1)** 140 (9) 3082-5.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198806
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880603
AB HL-60 cells, a human promyelocytic cell line, can be induced to differentiate along either **monocytic** or granulocytic pathways. The production of the second complement component, C2, is a marker of **monocytic** differentiation and can be up-regulated by cytokine stimulation. We studied the effects of **IFN-gamma** and vitamin D3, two factors previously shown to induce **monocytic** differentiation of HL-60 cells, on C2 production and C2 mRNA content. We found that HL-60 cells produce little if any C2 but can be induced to synthesize C2 by **IFN-gamma**. Vitamin D3 pretreatment followed by **IFN-gamma** stimulation resulted in earlier and greater production of C2. HL-60 cells did not contain detectable amounts of C2 mRNA unless they were stimulated with **IFN-gamma**. Pretreatment with vitamin D3 followed by **IFN-gamma** stimulation resulted in a 147% increase in C2 mRNA content compared with **IFN-gamma** stimulation alone. These results indicate that the up-regulation of C2 production by **IFN-gamma** and vitamin D3 is pretranslational although additional posttranslational effects were not excluded. C2 production by these cells is a useful marker of **monocytic** differentiation.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Cell Line
***Cholecalciferol: AD, administration & dosage**
*Complement 2: BI, biosynthesis
Dose-Response Relationship, Drug
Drug Administration Schedule
***Interferon Type II: AD, administration & dosage**
Monocytes: ME, metabolism
RNA, Messenger: ME, metabolism
Time Factors
Tumor Cells, Cultured
RN 67-97-0 (Cholecalciferol); **82115-62-6 (Interferon Type II)**
CN 0 (Complement 2); 0 (RNA, Messenger)

L73 ANSWER 38 OF 53 MEDLINE
AN 88171620 MEDLINE
DN 88171620 PubMed ID: 3127550
TI The determination of an immunologically active **dose** of **interferon-gamma** in patients with melanoma.
AU Maluish A E; Urba W J; Longo D L; Overton W R; Coggin D; Crisp E R; Williams R; Sherwin S A; Gordon K; Steis R G
CS Clinical Immunology Services, Program Resources, Inc., National Cancer Institute-Frederick Cancer Research Facility, MD 21701.
NC NO1-CO-23901 (NCI)
SO JOURNAL OF CLINICAL ONCOLOGY, **(1988 Mar)** 6 (3) 434-45.
Journal code: 8309333. ISSN: 0732-183X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 198805
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880503
AB This study was undertaken to determine an immunologically active regimen for the administration of recombinant **gamma-interferon** (rIFN-**gamma**). The patient population included patients with completely resected melanoma, stage I (Clark's level IV or V) or stage II. All patients exhibited no evidence of disease (NED) at the time of the study. Patients received rIFN-**gamma** by intramuscular (IM) injection daily for 15 days at 0.0001 mg/m2, 0.001 mg/m2, 0.01 mg/m2, 0.1 mg/m2 (ten patients/group), or 0.25 mg/m2 (five patients). **Interferon** (**IFN**) was well tolerated, with non-**dose**-limiting constitutional symptoms occurring in the majority of patients at 0.1 mg/m2 and 0.25 mg/m2. All five patients receiving 0.25 mg/m2 developed elevated transaminase levels, which led to a discontinuation of therapy in one patient. Immunological activity was assessed by serial measurements of natural killer (NK) cell activity, hydrogen peroxide production by **monocytes**, and changes in expression of Fc receptors and human leukocyte class II antigen (HLA-DR) on **monocytes**. These changes were determined at baseline (X2), six to seven time points during rIFN-**gamma** therapy, and two times after the last **dose** of rIFN-**gamma**. No changes were observed at the two lowest **doses**. At the 0.01 mg/m2 **dose**, all parameters were elevated but not as consistently nor to the same levels as seen following administration of 0.1 mg/m2. At 0.25 mg/m2, H2O2 production was enhanced, but unlike at 0.1 mg/m2, it declined during the last few days of **IFN** therapy. Subcutaneous (SC) administration was compared with IM administration using the 0.1 mg/m2 **dose**. SC administration resulted in enhanced H2O2 production and Fc receptor expression by **monocytes**. More consistent elevations in peroxide generation and higher levels of Fc receptor expression were seen following SC administration. No significant difference was found between the two routes of administration. A comparison of two schedules, daily and three times weekly, suggested that **monocyte** activation may return to normal 72 hours after **IFN** administration. Of the **doses** tested, 0.1 mg/m2 administered daily appeared to be the most effective biological response modifier (BRM) regimen, and because of ease of administration, we favor the SC route.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Dose-Response Relationship, Drug
Drug Administration Schedule
HLA-DR Antigens: AN, analysis
Hydrogen Peroxide: ME, metabolism
Injections, Intramuscular
Injections, Subcutaneous
***Interferon Type II: AD, administration & dosage**
Interferon Type II: AE, adverse effects
Killer Cells, Natural: IM, immunology
Melanoma: IM, immunology
***Melanoma: TH, therapy**
Monocytes: DE, drug effects
Monocytes: IM, immunology
Monocytes: ME, metabolism
Receptors, Fc: AN, analysis
RN 7722-84-1 (Hydrogen Peroxide); **82115-62-6 (Interferon Type II)**
CN 0 (HLA-DR Antigens); 0 (Receptors, Fc)

L73 ANSWER 39 OF 53 MEDLINE
AN 88109337 MEDLINE
DN 88109337 PubMed ID: 3123051

TI Divergent dose-related effects of **gamma-interferon** therapy on in vitro antibody-dependent cellular and nonspecific cytotoxicity by human peripheral blood **monocytes**.

AU Weiner L M; Steplewski Z; Koprowski H; Litwin S; Comis R L
CS Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111.

SO CANCER RESEARCH, **(1988 Feb 15)** 48 (4) 1042-6.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198803
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880314

AB Twenty-seven patients with advanced gastrointestinal malignancies received recombinant **gamma-interferon** (rIFN-**gamma**, Biogen) prior to treatment with the murine monoclonal antibody 17-1A (Centocor), which mediates human **monocyte** antibody-dependent cellular cytotoxicity (ADCC). rIFN-**gamma** was used because it enhances human **monocyte** Fc receptor expression, nonspecific **monocyte** cytotoxicity (NSMC) and ADCC in vitro. The study was designed to identify a rIFN-**gamma** dose with acceptable toxicities which enhanced NSMC and ADCC. Patients received one course of therapy consisting of rIFN-**gamma** by 4-h infusions daily for 4 days at doses ranging from 0.001 to 80.0 X 10(6) units/m2/d, followed by 400 mg of 17-1A on day 5. The maximally tolerated dose of rIFN-**gamma** in this study was 40 X 10(6) units/d. Significant toxicity was seen at the high (greater than 1 X 10(6) units) but not low (less than or equal to 1 X 10(6) units) dose levels. **Monocytes** were isolated from patients' peripheral blood at baseline and on Days 3 and 5 for cytotoxicity studies which measured 111-In release from SW1116 cells which bear the target antigen of 17-1A. **Low dose** rIFN-**gamma** enhanced NSMC by Day 5 as well as did high dose therapy. ADCC enhancement was seen with **low dose** therapy (% specific lysis on Day 5 = 23.5 +/- 6.4 SEM versus baseline of 9.6 +/- 3.3, P = 0.03), but not with high dose rIFN-**gamma** treatment. Total (i.e., NSMC + ADCC) **monocyte** cytotoxicity was equivalent in the low and high dose treatment groups, although ADCC contributed more to total values in the **low dose** group. These findings were particularly striking if **monocytes** were exposed to additional rIFN-**gamma** in vitro prior to incubation with labeled target cells. We conclude that **low dose** rIFN-**gamma** therapy is at least equivalent, and possibly superior to high doses in this setting. Furthermore, **low dose** therapy, supplemented by ex vivo incubation of purified **monocytes** with rIFN-**gamma**, may be an optimal treatment strategy for this cytokine.

CT Check Tags: Human
***Adenocarcinoma: IM, immunology**
Adenocarcinoma: TH, therapy
*Antibody-Dependent Cell Cytotoxicity
***Colonic Neoplasms: IM, immunology**
Colonic Neoplasms: TH, therapy
*Cytotoxicity, Immunologic
Dose-Response Relationship, Drug
Drug Evaluation
***Interferon Type II: TU, therapeutic use**
***Monocytes: IM, immunology**
***Pancreatic Neoplasms: IM, immunology**
Pancreatic Neoplasms: TH, therapy
***Rectal Neoplasms: IM, immunology**
Rectal Neoplasms: TH, therapy

Reference Values
RN **82115-62-6 (Interferon Type II)**

L73 ANSWER 40 OF 53 MEDLINE
AN 88076007 MEDLINE
DN 88076007 PubMed ID: 3120650
TI Use of recombinant **interferon gamma** administered intramuscularly for the treatment of psoriasis.
AU Morhenn V B; Pregerson-Rodan K; Mullen R H; Wood G S; Nickoloff B J; Sherwin S A; Farber E M
CS Department of Dermatology, Stanford (Calif) University.
SO ARCHIVES OF DERMATOLOGY, **(1987 Dec)** 123 (12) 1633-7.
Journal code: 0372433. ISSN: 0003-987X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198712
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871231
AB Twenty-three patients with chronic plaque-type psoriasis were treated with intramuscular administration of human recombinant **interferon gamma**. Patients were treated with **doses** of 0.01 to 0.25 mg/m2 daily (five out of seven days) for four weeks, or 0.25 mg/m2 three times weekly for one week with escalation to 0.5 mg/m2 for the subsequent seven weeks. Some patients treated with the 0.25-mg/m2 **dose** showed improvement coincident with their therapy. Although recombinant **interferon gamma** may have some therapeutic activity in certain patients' psoriasis, the magnitude of this effect is at best small. This result is in contrast to **interferon** alfa, which has been reported to cause an exacerbation of this disease. Staining of posttreatment biopsy specimens with a monoclonal antibody against HLA-DR antigen using an immunoperoxidase technique demonstrated HLA-DR expression by keratinocytes in some of the patients treated at the higher **doses**. No obvious correlation was seen between clinical improvement of the psoriasis and intensity or extent of HLA-DR antigen expression by keratinocytes in the skin biopsy specimens.
CT Check Tags: Human; Support, Non-U.S. Gov't
Biopsy, Needle
Dose-Response Relationship, Drug
Drug Evaluation
HLA-DR Antigens: AN, analysis
Immunoenzyme Techniques
Injections, Intramuscular
***Interferon Type II: AD, administration & dosage**
Interferon Type II: AE, adverse effects
Phenotype
Psoriasis: IM, immunology
Psoriasis: PA, pathology
***Psoriasis: TH, therapy**
Recombinant Proteins: AD, administration & dosage
Recombinant Proteins: AE, adverse effects
Skin: IM, immunology
Skin: PA, pathology
Time Factors
RN **82115-62-6 (Interferon Type II)**
CN 0 (HLA-DR Antigens); 0 (Recombinant Proteins)

L73 ANSWER 41 OF 53 MEDLINE
AN 88072649 MEDLINE
DN 88072649 PubMed ID: 3120433
TI [Treatment of condylomata acuminata with systemically administered

recombinant **gamma interferon**].
Behandlung von Condylomata acuminata mit systemisch appliziertem rekombinanten **Interferon-gamma**.
AU Fierlbeck G; Rassner G
CS Universitats-Hautklinik Tubingen.
SO ZEITSCHRIFT FUR HAUTKRANKHEITEN, **(1987 Sep 1)** 62 (17) 1280-7.
Journal code: 0367576. ISSN: 0301-0481.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 198801
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880106
AB 29 patients suffering from condylomata acuminata were systemically treated with human **gamma-interferon** obtained by means of gene technology. The daily **dose**, subcutaneous applied, amounted to 100 or 200 micrograms. 12 patients were completely cleared by surgical excision and additionally treated with **gamma-interferon** for 7 days. 3 of them developed recurrences. 17 patients were exclusively treated with **gamma-interferon** 100 or 200 micrograms daily; they underwent 6 courses of therapy, each lasting 7 days, with interruptions of 3-5 weeks of observation. As a result, 5 patients showed complete remission; 2 patients partially responded. The tolerance of the drug depended on the **dose**. We did not observe any toxic side effects. Our findings suggest that **gamma-interferon** subcutaneously given may be effective with genital warts.
CT Check Tags: Female; Human; Male
Adult
Combined Modality Therapy
Condylomata Acuminata: DT, drug therapy
***Condylomata Acuminata: TH, therapy**
Dose-Response Relationship, Drug
English Abstract
Genital Neoplasms, Female: DT, drug therapy
***Genital Neoplasms, Female: TH, therapy**
Genital Neoplasms, Male: DT, drug therapy
***Genital Neoplasms, Male: TH, therapy**
Injections, Subcutaneous
***Interferon Type II: AD, administration & dosage**
***Recombinant Proteins: AD, administration & dosage**
RN **82115-62-6 (Interferon Type II)**
CN 0 (Recombinant Proteins)

L73 ANSWER 42 OF 53 MEDLINE
AN 88061437 MEDLINE
DN 88061437 PubMed ID: 3119781
TI In vivo myelosuppression by combination **interferon** treatment: antagonism of MuIFN-**gamma** and MuIFN-beta myelosuppressive effects.
AU Naldini A; Fleischmann W R Jr
CS Department of Microbiology, University of Texas Medical Branch, Galveston 77550.
NC CA 26475 (NCI)
SO JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, **(1987 Oct)** 6 (5) 546-55.
Journal code: 8219656. ISSN: 0732-6580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198801

ED Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19880115

AB **Interferon** treatment has been shown to cause myelosuppression in man and in a mouse model. Combinations of **interferon-gamma** (**IFN-gamma**) with either **interferon**-alpha (**IFN**-alpha) or **interferon**-beta (**IFN**-beta) cause the synergistic enhancement of **interferons'** antiviral, antiproliferative, antitumor, and immunoregulatory activities. Thus, combinations of MuIFN-beta and either natural or recombinant DNA-derived MuIFN-**gamma** were evaluated for their ability to cause the synergistic enhancement of **interferon**'s myelosuppressive activity. The combinations of **interferons** were evaluated in vitro in bone-marrow colony-stimulating assays. They were seen to potentiate the in vitro myelosuppressive effect of the **interferons**. The combinations were evaluated for their in vivo myelosuppressive effect in mice. Treatment with the separate **interferons** caused a significant reduction in the number of circulating leukocytes, suggesting a potent myelosuppressive effect. However, treatment with the **interferons** in combination caused an antagonism and led to a myelosuppressive effect which was no greater than that of the **interferons** alone. The combinations of **interferons** were employed at concentrations which have been shown to provide substantial potentiation of the antitumor action of the **interferons** against B-16 melanoma. Thus, the data suggest that combination **interferon** therapy employing **IFN-gamma** together with either **IFN**-alpha or **IFN**-beta provide a potentiated antitumor activity without increasing the myelosuppressive side effect of the therapy.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Bone Marrow: DE, drug effects
Dose-Response Relationship, Drug
Hematopoietic Stem Cells: DE, drug effects
***Interferon Type I: AD, administration & dosage**
***Interferon Type II: AD, administration & dosage**
Mice
Mice, Inbred C57BL
Recombinant Proteins: AD, administration & dosage

RN **82115-62-6 (Interferon Type II)**

CN 0 (Interferon Type I); 0 (Recombinant Proteins)

L73 ANSWER 43 OF 53 MEDLINE

AN 87225055 MEDLINE

DN 87225055 PubMed ID: 3108462

TI Endogenous production of cytotoxic factor in mice induced by a combination of **interferon-gamma** and heterologous fibrinogen.

AU Kajikawa T; Inagawa H; Shimada Y; Satoh M; Oshima H; Abe S; Yamazaki M; Mizuno D

SO JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, **(1987 Apr)** 6 (2) 205-14.
Journal code: 8219656. ISSN: 0732-6580.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198707

ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19870710

AB The ability of heterologous fibrinogen in combination with **interferon** (**IFN**)-**gamma** to induce endogenous production of cytotoxic factor was examined. Heterologous but not

homologous fibrinogen induced high production of cytotoxic factor in **IFN-gamma**-primed mice. The cytotoxic activity was maximal 1 h after this triggering. The LD50 value of heterologous fibrinogen in mice was greater than 250 mg/kg i.v. But heterologous fibrinogen induced antibody, causing anaphylaxis. Therefore, the effect of successive injections of fibrinogens from a different species was tested. Cytotoxic factor could be produced repeatedly by successive treatments with a combination of **IFN-gamma** and heterologous fibrinogen from one species for 1 week, although the cytotoxic activity induced by successive injections gradually decreased. After the decrease of the triggering effect of heterologous fibrinogen of one species, heterologous fibrinogen from a different species could induce cytotoxic activity at the same level as that after the first triggering. Thus, a combination of **IFN-gamma** and heterologous fibrinogen is effective for cytotoxic factor production, provided different heterologous fibrinogens are used successively. This combination should be useful for endogenous cytotoxic factor production in clinical trials.

CT Check Tags: Animal
Cell Line
Cytotoxicity, Immunologic
Dose-Response Relationship, Drug
Drug Administration Schedule
Drug Synergism
***Fibrinogen: AD, administration & dosage**
Fibrinogen: TO, toxicity
***Interferon Type II: AD, administration & dosage**
Mice
Mice, Inbred C3H
*Proteins: BI, biosynthesis

RN **82115-62-6 (Interferon Type II)**; 9001-32-5 (Fibrinogen)
CN 0 (Proteins); 0 (killer factor)

L73 ANSWER 44 OF 53 MEDLINE
AN 87225050 MEDLINE
DN 87225050 PubMed ID: 3108460
TI Synergistic antiproliferative effect of recombinant alpha-**interferons** with recombinant **gamma-interferon**.
AU Hubbell H R; Craft J A; Leibowitz P J; Gillespie D H
NC P01 CA-29545 (NCI)
SO JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, **(1987 Apr)** 6 (2) 141-53.
Journal code: 8219656. ISSN: 0732-6580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198707
ED Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19870710
AB Two human tumor cell lines were studied for their response to the antiproliferative effect of recombinant human **interferons** (**IFNs**) alpha 2, alpha 4, a hybrid alpha (delta 4 alpha 2 Bgl II alpha 1), and **gamma**, individually and in combination. Natural human alpha-**IFN** was used as a reference point for all experiments. RT4 (bladder carcinoma) cells were overall more sensitive to the antiproliferative effects of the **IFNs** than A2182 (lung adenocarcinoma) cells. Three-way analysis of variance indicated that the relative effectiveness of the alpha-**IFNs** was alpha 2 less than alpha 4 less than hybrid alpha less than natural alpha-**IFN**. On an international reference unit per milliliter basis, **gamma-IFN** was 50- and 75-fold more effective than natural alpha-**IFN** and hybrid alpha-**IFN** in RT4 cells and 5.6-, 12.1-,

and 14.9-fold more effective than alpha 4-, hybrid alpha-, and natural alpha-**IFN** in A2182 cells. In contrast, when recalculated on a nanogram per milliliter basis, **gamma-IFN** was only threefold more effective than the hybrid alpha-**IFN** in RT4 and approximately twofold less effective than alpha 4 and the hybrid alpha in A2182. Combinations of alpha-**IFNs** gave additive or antagonistic effects. When any of the alpha-**IFNs** were combined with the **gamma-IFN**, however, a synergistic antiproliferative effect was seen. The magnitude of the synergy was dependent upon the concentration of **gamma-IFN** used and the type of alpha-**IFN** in the combination. Antagonistic effects were seen at the lowest **gamma-IFN** concentration studied (0.2 IRU/ml). Synergy also varied according to the potency of the alpha-**IFN** used.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Bladder Neoplasms: PA, pathology
Carcinoma: PA, pathology
*Cell Division: DE, drug effects
Cell Line
Dose-Response Relationship, Drug
Drug Synergism
***Interferon Type I: AD, administration & dosage**
***Interferon Type II: AD, administration & dosage**
Lung Neoplasms: PA, pathology
Recombinant Proteins: AD, administration & dosage

RN **82115-62-6 (Interferon Type II)**

CN 0 (Interferon Type I); 0 (Recombinant Proteins)

L73 ANSWER 45 OF 53 MEDLINE

AN 87224025 MEDLINE

DN 87224025 PubMed ID: 3108376

TI Synergistic effect of recombinant IL 2 and **interferon-gamma** on the proliferation of human monoclonal lymphocytes.

AU Karray S; Vazquez A; Merle-Beral H; Olive D; Debre P; Galanaud P

SO JOURNAL OF IMMUNOLOGY, **(1987 Jun 1)** 138 (11) 3824-8.
Journal code: 2985117R. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198707

ED Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19870702

AB We studied the effect of **interferon-gamma** (**IFN-gamma**) on the proliferation of lymphocytes from 10 B-type chronic lymphocytic leukemia (B-CLL) patients. In no instance did **IFN-gamma** induce a proliferative response whether used alone or in combination with anti-mu antibody (Ab). This was observed regardless of the responsiveness of a given patient's cells to interleukin 2 (IL 2) and to **B cell** growth factor (BCGF). In contrast **IFN-gamma** strongly and reproducibly synergized with IL 2 (but not with BCGF) to support B-CLL proliferation in five of the 10 patients. The effect of **IFN-gamma** was **dose** related and could be inhibited by an anti-**IFN-gamma** monoclonal Ab. A monoclonal Ab toward the IL 2 receptor molecule was also inhibitory. Preincubation with **IFN-gamma** potentiated the responsiveness of B-CLL to IL 2 in secondary cultures, showing that **IFN-gamma** exerts its effect before that of IL 2.

CT Check Tags: Human; Support, Non-U.S. Gov't
***B-Lymphocytes: PH, physiology**
Clone Cells: PH, physiology

Dose-Response Relationship, Drug
Drug Synergism
Growth Substances: PD, pharmacology
***Interferon Type II: AD, administration & dosage**
***Interleukin-2: AD, administration & dosage**
Interleukin-4
Kinetics
Leukemia, Lymphocytic: PA, pathology
*Lymphocyte Transformation
Lymphocyte Transformation: DE, drug effects
Lymphokines: PD, pharmacology
Recombinant Proteins
RN 207137-56-2 (Interleukin-4); **82115-62-6 (Interferon Type II)**
CN 0 (Growth Substances); 0 (Interleukin-2); 0 (Lymphokines); 0 (Recombinant Proteins)

L73 ANSWER 46 OF 53 MEDLINE
AN 87187161 MEDLINE
DN 87187161 PubMed ID: 3105867
TI Synergistic antitumor effects of tumor necrosis factor and **gamma -interferon** on human colon carcinoma cell lines.
AU Schiller J H; Bittner G; Storer B; Willson J K
SO CANCER RESEARCH, **(1987 Jun 1)** 47 (11) 2809-13.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198706
ED Entered STN: 19900303
Last Updated on STN: 19900303
Entered Medline: 19870625
AB We assessed the antiproliferative effects of tumor necrosis factor (TNF-alpha) and **gamma-interferon** (**IFN-gamma**) alone and in combination, on nine human colon carcinoma cell lines. All were resistant (less than 30% inhibition) to TNF-alpha alone. Four cell lines were resistant to **IFN-gamma** alone, two exhibited a minimal degree of sensitivity (30-50% inhibition), one was moderately sensitive, and two were inhibited 70% or greater. A synergistic antiproliferative effect occurred in eight of the nine cell lines treated with a combination of TNF-alpha and **IFN-gamma**. In seven of these eight, the combination of cytokines resulted in 30-40% more growth inhibition than predicted had an additive interaction occurred (P less than 0.005). In two cell lines with an induced resistance to mitomycin C, an increase in resistance to combined TNF-alpha and **IFN-gamma** treatment correlated with an increasing resistance to mitomycin C. The data were further analyzed to determine if combination treatment altered the sensitivity of the cells to one or both agents in addition to synergistically potentiating growth inhibitory effects. Combinations of TNF-alpha/**IFN-gamma** enhanced the **dose** response activity of TNF-alpha in three cell lines (P less than or equal to 0.09) and decreased the **dose** response activity of **IFN-gamma** in another three (P less than or equal to 0.02). Colony forming experiments on HCT 116 cells demonstrated a reduction in the number of 250-micron colonies in the **IFN-gamma**/TNF-alpha treatment groups when compared to controls, indicating that combined treatment had a cytotoxic effect. We conclude that combination TNF-alpha/**IFN-gamma** treatment has a synergistic cytotoxic effect on human colon carcinoma cells. **IFN-gamma** may enhance the effectiveness of TNF-alpha in some cell lines, but not conversely. These results may have therapeutic implications.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't,

Non-P.H.S.
Cell Cycle: DE, drug effects
Cell Line
***Colonic Neoplasms: TH, therapy**
Dose-Response Relationship, Drug
Drug Synergism
***Glycoproteins: AD, administration & dosage**
Growth Inhibitors
Immunotherapy
***Interferon Type II: AD, administration & dosage**
Tumor Necrosis Factor
RN **82115-62-6 (Interferon Type II)**
CN 0 (Glycoproteins); 0 (Growth Inhibitors); 0 (Tumor Necrosis Factor)

L73 ANSWER 47 OF 53 MEDLINE
AN 87078050 MEDLINE
DN 87078050 PubMed ID: 3098417
TI Phase I study of i.v. administered recombinant **gamma interferon** in cancer patients.
AU Kurzrock R; Quesada J R; Rosenblum M G; Sherwin S A; Gutterman J U
SO CANCER TREATMENT REPORTS, **(1986 Dec)** 70 (12) 1357-64.
Journal code: 7607107. ISSN: 0361-5960.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198701
ED Entered STN: 19900302
Last Updated on STN: 19970203
Entered Medline: 19870130
AB We report a phase I study of the biological effects, tolerance, and pharmacokinetics of 6- and 24-hour iv infusions of recombinant **interferon-gamma** (rIFN-**gamma**) in cancer patients. Twenty-one patients received the 6-hour iv infusion regimen at **doses** ranging from 0.016 to 0.65 mg/m2/day. Forty-one patients received the 24-hour iv infusion regimen at **doses** ranging from 0.01 to 0.05 mg/m2/day. Fever and flu-like symptoms were the most common side effects and were seen at all **dose** levels. The maximum tolerated **dose** was 0.16 mg/m2 for the 6-hour regimen and 0.01 mg/m2/day for the 24-hour regimen. A **dose**-dependent granulocytopenia was observed at **doses** greater than or equal to 0.05 mg/m2/day. A marked increase in beta2 microglobulin occurred by Day 5 of treatment in almost all patients, regardless of the **dose** level. Consistent serum levels of rIFN-**gamma** were achieved only at **doses** of 0.325 mg/m2/day of the 6-hour infusion. The mean serum concentrations at this **dose** ranged from 18 to 83 units/ml as measured by bioassay (0.64-2.4 ng/ml by enzyme-linked immunoassay). Antibody against rIFN-**gamma** did not develop in any patient. During the short period of evaluation of this study, one patient with renal cell carcinoma achieved a partial response, and three patients with renal cell (two) and lung carcinoma (one), respectively, achieved minor responses. This study will form the framework for phase II efficacy trials of iv rIFN-**gamma**.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Antibodies: AN, analysis
Dose-Response Relationship, Drug
Drug Administration Schedule
Drug Evaluation
***Interferon Type II: AD, administration & dosage**

Interferon Type II: AE, adverse effects
Kinetics
Middle Age
Neoplasm Metastasis
Neoplasms: BL, blood
Neoplasms: PA, pathology
***Neoplasms: TH, therapy**
***Recombinant Proteins: AD, administration & dosage**
Recombinant Proteins: AE, adverse effects
Research Design
beta 2-Microglobulin: AN, analysis
RN **82115-62-6 (Interferon Type II)**
CN 0 (Antibodies); 0 (Recombinant Proteins); 0 (beta 2-Microglobulin)

L73 ANSWER 48 OF 53 MEDLINE
AN 86302606 MEDLINE
DN 86302606 PubMed ID: 3091476
TI Biologic effects of **gamma interferon** pre-treatment followed by monoclonal antibody 17-1A administration in patients with gastrointestinal carcinoma.
AU Weiner L M; Steplewski Z; Koprowski H; Sears H F; Litwin S; Comis R L
SO HYBRIDOMA, **(1986 Jul)** 5 Suppl 1 S65-77.
Journal code: 8202424. ISSN: 0272-457X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198610
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19861015
AB Twenty-seven patients with metastatic adenocarcinoma of the colon or pancreas were treated with 400mg of monoclonal antibody 17-1A. This antibody, which binds to a cell surface glycoprotein moiety preferentially expressed by adenocarcinomas of the rectum, colon, pancreas, and stomach, is postulated to induce antibody-dependent **monocyte** cytotoxicity (ADMC) as a mechanism of tumor lysis. Therapy was preceded by four days of **gamma interferon** infusions, with the intent of activating peripheral blood **monocytes**, enhancing **monocyte** Fc receptor expression and increasing the likelihood of tumor lysis as reflected by enhanced ADMC directed against a colon carcinoma cell line (SW1116) which expresses 17-1A's target antigen. In this Phase I study patients were treated daily at one of the following **gamma interferon** dose levels (X 10(6) U/M2/day): 0.001, 0.01, 0.1, 1.0, 10.0, 40.0, 60.0, 80.0. Addition of 100 U/ml of rIFN-**gamma** in vitro to **monocytes** isolated from normal controls or from patients prior to treatment significantly enhanced **monocyte** Fc receptor expression and ADMC. in vitro tumor cell killing by **monocytes** and monoclonal antibody was enhanced by treatment with **low doses** of rIFN-**gamma**, while treatment with high doses of rIFN-**gamma** did not enhance ADMC. No objective clinical responses were noted, although serum tumor markers dropped transiently in 36% of the treated patients. Seven of 11 assayed patients developed human anti-idiotype antibodies. With better scheduling of rIFN- and 17-1A we hope to duplicate optimal in vitro conditions for antibody-mediated cytotoxicity, hopefully enhancing in vivo antibody mediated tumor lysis.
CT Check Tags: Human
***Adenocarcinoma: TH, therapy**
*Antibodies, Monoclonal: TU, therapeutic use
Antibodies, Monoclonal: TO, toxicity
Cytotoxicity, Immunologic
Drug Evaluation

Immunotherapy
***Interferon Type II: TU, therapeutic use**
Monocytes: IM, immunology
***Pancreatic Neoplasms: TH, therapy**
Receptors, Fc: AN, analysis
RN **82115-62-6 (Interferon Type II)**
CN 0 (Antibodies, Monoclonal); 0 (Receptors, Fc)

L73 ANSWER 49 OF 53 MEDLINE
AN 86252596 MEDLINE
DN 86252596 PubMed ID: 2425014
TI Human alpha- and beta-**interferon** but not **gamma**-
suppress the in vitro replication of LAV, HTLV-III, and ARV-2.
AU Yamamoto J K; Barre-Sinoussi F; Bolton V; Pedersen N C; Gardner M B
NC CA-39016-01 (NCI)
SO JOURNAL OF INTERFERON RESEARCH, **(1986 Apr)** 6 (2) 143-52.
Journal code: 8100396. ISSN: 0197-8357.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 198607
ED Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860731
AB The effect of human **interferons** (**IFNs**) (alpha, beta,
and **gamma**) on the in vitro replication of AIDS viruses (LAV,
HTLV-III, and ARV-2) in human peripheral blood lymphocytes was
investigated. At the time of peak virus production, **IFN**-alpha
preparations (leukocyte, Namalwa, alpha 1, and alpha 2) at 100 U/ml,
suppressed LAV, HTLV-III, and ARV-2 replication as measured by reverse
transcriptase (RT) activity by greater than 50%. This suppression was dose
dependent and high dosages (500 U/ml) of **IFN**-alpha resulted in
almost complete suppression of RT activities (77-99%). A **low**
dose (100 U/ml) of **IFN**-beta suppressed all three AIDS
viruses by 75%. In contrast, human **IFN-gamma** at a dose
range from 100 U/ml to 500 U/ml had no significant effect on the
production of infectious viruses. These results indicate that only
IFN-alpha and -beta are effective against LAV, HTLV-III, and ARV-2
replication. A continuous supply of **IFN** appeared to be essential
for the constant suppression of RT activity. In fact, upon termination of
single **IFN** treatment, enhanced virus production resulted.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
***Acquired Immunodeficiency Syndrome: MI, microbiology**
*Deltaretrovirus: DE, drug effects
Deltaretrovirus: PH, physiology
Dose-Response Relationship, Drug
*Interferon Type I: PD, pharmacology
***Interferon Type II: PD, pharmacology**
Reverse Transcriptase Inhibitors
*Virus Replication: DE, drug effects
RN **82115-62-6 (Interferon Type II)**
CN 0 (Interferon Type I); 0 (Reverse Transcriptase Inhibitors)

L73 ANSWER 50 OF 53 MEDLINE
AN 86133239 MEDLINE
DN 86133239 PubMed ID: 3081255
TI Effect of hyperthermia on combination interferon treatment: enhancement of
the antiproliferative activity against murine B-16 melanoma.
AU Fleischmann W R Jr; Fleischmann C M; Gindhart T D
NC CA26475 (NCI)
SO CANCER RESEARCH, **(1986 Apr)** 46 (4 Pt 1) 1722-6.
Journal code: 2984705R. ISSN: 0008-5472.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198604
ED Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860423
AB Previous studies have evaluated the effects of hyperthermia on the antiproliferative activity of **interferon**. The activities of all three types of **interferon** have been shown to be synergistically enhanced by hyperthermic conditions. Further, the antiproliferative activity of **interferon** has been shown to be synergistically enhanced by combinations of **gamma**-plus alpha- or beta-**interferon**. The question remained whether combining these two methods of enhancing **interferon** activity would lead to an even higher level of enhancement of antiproliferative activity or to an antagonism of their separate effects. To address this question, mouse B-16 melanoma cells were cloned at 37.3 degrees C and at 39.4 degrees C in the presence of various combinations of murine alpha/beta- and **gamma -interferon**. Potentiation of **interferon**'s antiproliferative activity by combination **interferon** treatment was found to occur at both temperatures. Moreover, the level of potentiation was synergistically enhanced by hyperthermic conditions. The results suggest that a combined treatment regimen of hyperthermia and combination **interferon** therapy (**gamma**- plus alpha- or beta-**interferon**) may provide a highly potent antitumor effect.
CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Cell Division: DE, drug effects
Cells, Cultured
Dose-Response Relationship, Drug
Drug Combinations
*Heat
***Interferon Type I: AD, administration & dosage**
***Interferon Type II: AD, administration & dosage**
***Melanoma: PA, pathology**
Mice
RN **82115-62-6 (Interferon Type II)**
CN 0 (Drug Combinations); 0 (Interferon Type I)

L73 ANSWER 51 OF 53 MEDLINE
AN 85291924 MEDLINE
DN 85291924 PubMed ID: 3928825
TI Therapeutic trial of **interferon-gamma** in patients with epidemic Kaposi's sarcoma.
AU Krigel R L; Odajnyk C M; Laubenstein L J; Ostreicher R; Wernz J; Vilcek J; Rubinstein P; Friedman-Kien A E
NC CA-06927 (NCI)
CA-16087 (NCI)
SO JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, **(1985 Aug)** 4 (4) 358-64.
Journal code: 8219656. ISSN: 0732-6580.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198510
ED Entered STN: 19900320
Last Updated on STN: 19980206
Entered Medline: 19851015
AB An epidemic form of Kaposi's sarcoma associated with the acquired immune deficiency syndrome has been recently described. Seven homosexual men with

biopsy-documented epidemic Kaposi's sarcoma were treated with a human **interferon-gamma** preparation. All patients had generalized disease. Only one patient had received prior chemotherapy, and one other patient had recovered from a prior opportunistic infection. **Interferon-gamma** was administered in a dose of 500,000 U intramuscularly daily, with two 10-day induction courses, separated by a 2-week medication-free period. This was followed by maintenance therapy in the same dose twice weekly. Toxicities consisted of a flu-like illness with high fevers, shaking chills, myalgias, and arthralgias. There were no complete or partial responses. All patients exhibited disease progression, with a rapid progression of previously stable disease necessitating discontinuation of therapy in three patients. We conclude that **low doses** of this human **interferon-gamma** preparation are ineffective in epidemic Kaposi's sarcoma.

CT Check Tags: Comparative Study; Human; Male; Support, U.S. Gov't, P.H.S.
Adult
Antibodies: AN, analysis
Clinical Trials
Homosexuality
Interferon Type II: IM, immunology
***Interferon Type II: TU, therapeutic use**
Middle Age
Sarcoma, Kaposi: IM, immunology
***Sarcoma, Kaposi: TH, therapy**
Skin Tests

RN **82115-62-6 (Interferon Type II)**
CN 0 (Antibodies)

L73 ANSWER 52 OF 53 MEDLINE
AN 85181791 MEDLINE
DN 85181791 PubMed ID: 6241930
TI A phase 1 study of recombinant **interferon-gamma** given intravenously by portable mini-pump: a preliminary report.
AU Sriskandan K; Garner P; Watkinson J; Gerlis L; Tee D E
SO INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY RESEARCH, **(1984)** 4 (6) 469-74.
Journal code: 8110183. ISSN: 0251-1649.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198506
ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850606
AB Recombinant **interferon-gamma** was given to patients with tumours by a six-hour intravenous infusion using a portable mini-pump, to assess the side-effects of the drug. At present, 11 patients have been treated; 2 adenocarcinoma of the ovary, 3 squamous carcinoma of the bronchus, 1 adenocarcinoma of the breast, 1 adenocarcinoma of the stomach, 1 Hodgkin's lymphoma, 1 case of two primaries, adenocarcinoma of the breast and ovary, and 1 adenocarcinoma of unknown origin. Two patients received 1 X 10(6) units/m2/infusion, four received 3 X 10(6) U/m2/inf., three received 6 X 10(6) U/m2/inf. and two received 9 X 10(6) U/m2/inf. Two further **dose** levels will be used in the future; 27 and 51 X 10(6) U/m2/inf. Three 6-hour infusions a week were given for a four week period. The major side-effects of **gamma-interferon** were **dose**-related pyrexia with rigors to which there was no tachyphylaxis, acute and chronic tiredness, nausea with or without vomiting, headache, backache and myalgia. There was also a **dose**-dependent immediate but mild and transient decrease in the total white cell count. All effects have been transient, and none have been severe. We have also noticed that intravenous infusions by mini-pumps are tolerated

far better by the patients than conventional drip systems, and we feel mini-pumps are the ideal way to give intravenous infusions.

CT Check Tags: Human
Adult
Aged
Back Pain: ET, etiology
Dose-Response Relationship, Drug
Drug Evaluation
Fever: ET, etiology
Headache: ET, etiology
Infusions, Parenteral: IS, instrumentation
***Interferon Type II: AD, administration & dosage**
Interferon Type II: AE, adverse effects
Interferon Type II: TU, therapeutic use
Middle Age
Nausea: ET, etiology
***Neoplasms: TH, therapy**

RN **82115-62-6 (Interferon Type II)**

L73 ANSWER 53 OF 53 MEDLINE
AN 85082134 MEDLINE
DN 85082134 PubMed ID: 6096507
TI Potentiation of **interferon**'s antiviral activity by the mutually synergistic interaction of MuIFN-alpha/beta and MuIFN-**gamma**.
AU Schwarz L A; Fleischmann C M; Fleischmann W R Jr
NC CA 26475 (NCI)
SO JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, **(1984 Dec)** 3 (6) 608-12.
Journal code: 8219656. ISSN: 0732-6580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198502
ED Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850221
AB The interaction of the **interferons** (**IFNs**) that cooperate to potentiate the antiviral action of **IFN** was studied. Serial dilutions of MuIFN-**gamma** and MuIFN-alpha/beta were employed separately and in combination to block virus replication in one-step, virus yield reduction experiments. To calculate the potentiation of **IFN** activity, protection levels obtained for each combination of MuIFN-**gamma** and MuIFN-alpha/beta were compared with those obtained for the separate **IFNs**. Potentiation levels increased with increasing concentrations of each of the **IFNs** in a **dose**-dependent manner, suggesting that potentiation of **IFN**'s antiviral activity was the result of the mutually synergistic interaction of the **IFNs**. Three challenge viruses were employed: Mengo virus (positive-strand RNA virus), vesicular stomatitis virus (negative-strand RNA virus), and vaccinia virus (DNA virus). Identical results were observed with the three different viruses, suggesting that mutual synergism was a basic feature of the potentiation of **IFN**'s antiviral activity by combined preparations of MuIFN-**gamma** and MuIFN-alpha/beta.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Dose-Response Relationship, Drug
Drug Synergism
***Interferon Type I: AD, administration & dosage**
***Interferon Type II: AD, administration & dosage**
Mengovirus: GD, growth & development
Mice
Vaccinia virus: GD, growth & development

Vesicular stomatitis-Indiana virus: GD, growth & development
*Viral Interference
Virus Replication: DE, drug effects
RN **82115-62-6 (Interferon Type II)**
CN 0 (Interferon Type I)

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L119 ANSWER 1 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2002-436795 [47] WPIX
DNC C2002-124252
TI Inducing differentiation of immature dendritic cells, for use in vaccines for immunotherapy of cancer, comprises ex vivo treatment with heat-shock protein 70.
DC B04 D16
IN GASTPAR, R; ISSELS, R D; KUPPNER, M
PA (GSFU-N) GSF FORSCHUNGSZENTRUM UMWELT & GESUNDHEI
CYC 26
PI DE 10115439 A1 20020516 (200247)* 17p C12N005-08
EP 1209226 A2 20020529 (200247) EN C12N005-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT DE 10115439 A1 DE 2001-10115439 20010329; EP 1209226 A2 EP 2001-125374 20011030
PRAI DE 2000-10055213 20001107
IC ICM C12N005-06; C12N005-08
ICS A61K035-14; A61K038-17; A61P035-00; C07K014-47
AB DE 10115439 A UPAB: 20020725
NOVELTY - Ex vivo method for inducing TNF alpha (tumor necrosis factor alpha)-free differentiation of immature dendritic cells (DC) to mature DC by treatment with a protein (I) of the heat-shock protein (hsp) 70 family,

or its biologically active fragment.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a mature DC produced this way; and

(2) a therapeutic composition, containing (I) or its fragment as the only active component, for inducing maturation of immature DC.

ACTIVITY - Cytostatic. No biological data is given.

MECHANISM OF ACTION - Vaccine; specific CTL (cytotoxic T lymphocyte) response against tumor antigens inducer. DC from compatible donors were stimulated in presence of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-4 (IL-4) and 0.5 micro g/ml recombinant hsp70 for 8 days, then pulsed with 10 micro g/ml of a tyrosinase-derived, HLA-A asterisk 0201-restricted nonapeptide. When the treated cells were incubated with A asterisk 0201-restricted T cells, specific for the nonapeptide, proliferation (in a tritiated thymidine incorporation assay) was 2400 counts per minute (cpm), compared with 1500 for cells stimulated with GM-CSF and IL-4 only, and about 400 for the T cells alone. Production of **interferon gamma** was also higher in the hsp70-treated cells.

USE - The mature DC, or a TNFa-free composition containing (I) or its fragment, are useful in vaccines for immunotherapy of a wide range of cancers, particularly solid tumors.

ADVANTAGE - Unlike known methods of maturing DC, this process does not require toxic TNFa, produces mature DC with high capacity to present antigens to T cells, and (I) is more effective than TNFa, even at **low doses**.

Dwg.0/8

FS CPI

FA AB; DCN

MC CPI: B04-B04C1; B04-B04C2; B04-C01B; B04-F01; B04-F04; B04-H01; B04-H0100E; B04-H02D; B04-H04C; B04-L01; **B14-H01**; B14-S11; D05-H07; D05-H08

TECH UPTX: 20020725

TECHNOLOGY FOCUS - BIOLOGY - Preferred Materials: The active fragment of (I) is particularly the C-terminal domain of hsp70.

Preferred Cells: Immature DC are generated by culturing monocytes in an induction medium containing granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4), each present at 500 - 1000 units/ml. The monocytes are from human blood and are particularly plastic-adherent cells.

Preferred Process: Treatment is particularly with recombinant hsp70 at 0.1 - 1, preferably 0.5 micrograms/ml, and the matured DC formed may be pulsed with a tumor or viral antigen, e.g. the 369 - 377 amino acid fragment of tyrosinase.

L119 ANSWER 2 OF 31 WPIX (C) 2002 THOMSON DERWENT

AN 2002-147237 [19] WPIX

DNC C2002-045577

TI Use of **low dose** of **interferon-gamma** (**IFN-gamma**) for the treatment or prevention of **IFN-gamma** sensitive disease such as acute inflammation.

DC B04

IN **AMENTO, E P; CUMMINS, J M**

PA (AMAR-N) AMARILLO BIOSCIENCES INC; (MOLE-N) MOLECULAR MEDICINE RES INST

CYC 93

PI WO 2001023006 A1 20010405 (200219)* EN 30p A61K049-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000077317 A 20010430 (200219) A61K049-00

ADT WO 2001023006 A1 WO 2000-US26750 20000928; AU 2000077317 A AU 2000-77317 20000928
FDT AU 2000077317 A Based on WO 200123006
PRAI US 1999-156480P 19990928
IC ICM A61K049-00
ICS A01N037-18; **A61K038-00; A61K038-21**
AB WO 200123006 A UPAB: 20020321
NOVELTY - A method for treatment or prevention of **interferon** (**IFN**)-**gamma** sensitive disease involves administering **IFN-gamma** (0.1 - 1000 international unit (IU)/kg) to patient.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a formulation comprising human **IFN-gamma** (10 - 50000 IU) in unit dosage form about of and a carrier.

ACTIVITY - Antiinflammatory; cytostatic; tranquilizer; vulnerary; antiasthmatic; osteopathic; fungicide; antibacterial; antianemic; immunomodulator; dermatological; immunosuppressive.

No biological data given.

MECHANISM OF ACTION - B-cell population activator.

USE - For treating or preventing **IFN-gamma** sensitive disease states e.g. inflammation (preferably acute inflammation e.g asthma), diseases resulting from monocyte, neutrophil and B-cell dysfunction, cancer, fibrosis, chronic granulomatosis disease and osteopetrosis, fibrosis of any organ.

Also for treating bacterial or fungal disease in human. The acute inflammation is induced by radiation of the lungs, brain or kidney during radiation therapy for tumors, or results from reperfusion injury incident, is induced by a traumatic injury to the brain or spinal cord and traumatic burns (all claimed).

For activating the B-cell population of a patient suffering from a disease state (all claimed) e.g. acquired immunodeficiency syndrome, xeroderma pigmentosa, severe combined immunodeficiencies, agammaglobulinemias, multiple myeloma, leukemia.

The fibrosis includes interstitial joint and interstitial lung diseases. For treating the diseases of the lower bronchial or alveolar lining. The other inflammatory disorders are Chediak-Higashi syndrome, Job's syndrome, systemic lupus erythematosus or aplastic anemia.

ADVANTAGE - The treatment provides **low doses** of **IFN-gamma** and thus effects similar to those produced by a given daily dosage administered for a given number of days can be achieved by administering lower dosage for a great number of days, or a higher dosage for a smaller number of days.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: **B04-H05C; B14-A01; B14-A04A; B14-C03; B14-H01; B14-K01; B14-K01A; B14-N01**
TECH UPTX: 20020321
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The formulation is in liquid or solid form. The carrier comprises **saliva-soluble** solid and the formulation is in **lozenge** dosage form.
The formulation further comprises therapeutic agent selected from an antibiotic, an antifungal, an antifibrotic or a chemotherapeutic agent known for use in cancer therapy or for treatment of immune diseases characterized by hypoactive or hyperactive immune system dysfunction.

L119 ANSWER 3 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2001-564233 [63] WPIX
DNC C2001-167411
TI Promoting weight loss comprises administering mixture of alpha-**interferon** and **gamma-interferon**.

DC B04
IN ERICSSON, A D
PA (RXIB-N) RX/IBR CORP
CYC 1
PI US 6270756 B1 20010807 (200163)* 4p A61K038-21 <--
ADT US 6270756 B1 US 1999-385989 19990830
PRAI US 1999-385989 19990830
IC ICM **A61K038-21**
ICS A61K035-12; A61K035-26; A61K035-32; A61K035-36
AB US 6270756 B UPAB: 20011031
NOVELTY - Promoting weight loss comprises administering a mixture (I) of alpha -**interferon** and **gamma** -**interferon**
which causes production and release of zinc- alpha 2-glycoproteins from lymphocytes and stimulates lipid breakdown and reduction of fat stores. The zinc- alpha 2-glycoproteins have a tendency to precipitate zinc salts and exhibit electrophoretic mobility in the region of alpha -2 globulins.
ACTIVITY - Anorectic.
17 Normal obese adults with initial weight of 128-338 pounds and a mean of 215.7 pounds were each instructed not to diet and to live a normal life and in addition to use ObeX (comprising 3 million units of alpha **interferon** and 3 million units **gamma interferon**
in 2 liters of sterile phosphate buffer solution) spray three times per day and report weight/girth frequently. One-two weeks later the weight ranged from 128-319 pounds, with a mean of 207.4 pounds. There were no reported side effects and the overall mean weight loss for the group of subjects was 8.3 pounds. 1-5 inches was lost in the girth as measured at the waist.
MECHANISM OF ACTION - (I) Actuates production and release of zinc alpha -2-glucoprotein.
USE - Used for promoting weight loss.
ADVANTAGE - The method is more effective in causing weight loss in humans than fasting. Weight loss during the initial period is at a greater rate than that caused by fasting.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-H05A; **B04-H05C**; B14-E12; B14-G03
TECH UPTX: 20011031
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred composition: The composition is administered in the form of spray, capsule, tablet or **lozenge**. The spray has a volume of 0.1 ml and contains 150 units each of alpha-**interferon** and **gamma-interferon**
.

L119 ANSWER 4 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2001-514501 [56] WPIX
DNC C2001-153732
TI Composition comprising a combination of an oxidizing and/or reducing agent, a protein-denaturing agent, and a hapten, useful for treating neoplasms, tumors, and cancers.
DC B05 D16
IN YU, B
PA (YUBB-I) YU B
CYC 94
PI WO 2001052868 A1 20010726 (200156)* EN 83p A61K033-40
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001030977 A 20010731 (200171) A61K033-40
US 2002044919 A1 20020418 (200228) A61K039-395

ADT WO 2001052868 A1 WO 2001-US1737 20010118; AU 2001030977 A AU 2001-30977 20010118; US 2002044919 A1 Provisional US 2000-177024P 20000119, US 2001-765060 20010117
FDT AU 2001030977 A Based on WO 200152868
PRAI US 2000-177024P 20000119; US 2001-765060 20010117
IC ICM A61K033-40; A61K039-395
ICS A61K031-045; A61K031-06; A61K031-45; A61K031-724; **A61K038-19**; **A61K038-20**; **A61K038-43**; A61K048-00; A61P035-00
AB WO 200152868 A UPAB: 20011001
NOVELTY - A composition (I) comprising a combination of an oxidizing or reducing agent, a protein-denaturing agent, and a hapten, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a kit comprising the combination (I);

(2) an article of manufacture comprising:

(a) packaging material;

(b) the combination above; and

(c) a label indicating that the article is for treating neoplasms; and

(3) a method for treating neoplasm in a mammal comprising in situ administration to the neoplasm of a mammal, a hapten and a coagulation agent or treatment that causes coagulation of the neoplasm (an autologous immune response is generated against the neoplasm).

ACTIVITY - Cytostatic.

31 advanced stage IV liver cancer patients were treated using the new combination. Prior to procedure, patients were given a mild sedative or painkiller. Patients were calmed thoroughly and were also monitored by modern medial imaging. With local anesthesia, percutaneous puncture was administered directly into the tumor using a spinal needle connected to a high-power syringe containing a combination of ethanol, H2O2, anticancer drug AraC (8 mg/ml) and hemotoxilin (5 mg/ml). Combination was injected directly into the tumor and distributed throughout the matrix of the whole tumor. Sonic imaging showed the stranger echo imaging which indicated the coagulation area.

Following coagulation lysis and tumor cell death monitored by sonic imaging, which showed liquefied echo, tumor started to shrink and disappear. Normal tissues grew replacing the tumor. The process was monitored by medical imaging systems. The amount of the ingredients of the combination injected into the tumor was determined by the diameter of tumors (cm) with 2 ml of the combination for each centimeter.

Procedure was repeated in 1-2 weeks. On average, each patient was treated with the injection for 3 times. No severe side effects for all the treated patients was observed, although some patients experienced tolerable pain the injection site while a few had light fever during the first week. All side effects disappeared in about 1 week. No serious complications happened in any cases.

MECHANISM OF ACTION - Gene therapy.

USE - The combination and the methods are useful for treating neoplasms, tumors, and cancers, including neoplasm or cancer of the e.g. adrenal gland, anus, auditory nerve, bile ducts, bladder, bone, brain, breast, bruccal, central nervous system, cervix, colon, ear, endometrium, esophagus, eye, eyelids, fallopian tube, gastrointestinal tract, head and neck, heart, kidney, larynx, liver, lung, or mandible.

The combination and methods may further be used in treating tumors of mesenchymal origin (e.g. connective tissue and derivatives, or endothelial and related tissues blood vessels), epithelial origin (stratified squamous carcinoma, or basal cells of skin or adenexa), and tumors derived from more than one neoplastic cell types derived from more than one germ layers.

The treatment may be used with radiation therapy, before surgery for the pre-treatment of neoplasm for easier removal of the neoplastic mass and reduces the neoplasm metastasis rate, or with gene therapy.

Dwg.0/4

FS CPI
FA AB; DCN
MC CPI: B01-B03; B01-C01; B01-C02; B02-M; B03-A; B04-C02X; B04-H05A; B05-A03B; B05-B01J; B06-H; B07-H; B10-A13C; B10-A17; B10-B02D; B10-B02E; B10-C02; B10-C04C; B10-E02; B10-E03; **B14-H01**; D05-H07; D05-H08
TECH UPTX: 20011001

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Combination: The oxidizing or reducing agent, protein denaturing agent, and hapten are formulated in a single pharmaceutical composition, or each is formulated in a separate pharmaceutical composition.

The oxidizing agent is selected from hydrogen peroxide, ozone, polyatomic oxygen O7, polyatomic oxygen O8, NaIO4, potassium peroxymonosulfate (oxone), D,L-S-methyllipoic acid methyl ester, tertiary butyl hydroperoxide, menadione, diamide, iodogen, N-bromosuccinimide, omeprazole, and N-ethylmaleimide. The reducing agent is selected from hematoxylin, a hypoxic reducing agent, and non-nitro compound tirapazamine (SR4233).

The hypoxic reducing agent is nitroimidazole. The protein-denaturing agent is an alcohol, guanidine hydrochloride, guanidinium thiocyanate, sodium citrate, 2-mercaptoethanol, the ionic detergent sarcoxyl, phenol, chloroform or urea.

The alcohol is methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-decyl, n-dodecyl, n-tetradecyl, n-hexadecyl, n-octadecyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, active-amyl, tert-pentyl, cyclopentanol, cyclohexanol, allyl, crotyl, methylvinylmethanol, benzyl, alpha-phenylethyl, beta-phenylethyl, diphenylmethanol, triphenylmethanol, cinnamyl, 1,2-ethanediol, 1,2-propanediol, 1,3-propanediol, glycerol, and pentaerythritol alcohol, preferably ethanol. The hapten is selected from trinitrophenol (TNP), dinitrophenyl (DNP), N-iodoacetyl-N'-(5-sulfonic 1- naphtyl) ethylene diamine (AED), dinitrofluorobenzene (DNFB), and ovabulin (OVA).

The composition further comprises an anti-neoplasm agent, preferably an anti-angiogenic agent, which may consist of an inhibitor of basement membrane degradation, cell migration, endothelial cell proliferation, three-dimensional organization, or establishment of potency.

The anti-angiogenic agent is selected form an angiostatic gene, angiostatic chemokine gene, AGM-1470 (TNP-1470), angiostatic steroids, angiostatin, antibodies against avbeta3, bFGF, IL-1, TNF-alpha, or VEGF, auranofin, azathipprine, BB-94, BB-2516, basic FGF-**soluble** receptor, carboxyamido-trizole, cartilage-derived inhibitor, chitin, chloroquine, cisplatin, CM 101, cortisone/heparine, cortisone/hyaluroflan, cortexolone/heparin, CT-2584cyclosphosphamide, cyclosporin A, dexamethasone, diclofenac/hyaluronan, eosinophilic major basic protein, fibronectin peptides, gelatinase inhibitor, glioma-derived angiogenesis inhibitory factor, GM-1474, gold chloride, gold thiomalate, heparinases, hyaluronan (high and low molecular-weigh t species), hydrocortisone/beta-cyclodextran, ibuprofen, indomethacin, **interferon**-alpha, **interferon gamma**-inducible protein 10, **interferon-gamma**, IL-1, IL-2, IL-4, IL-12, laminin, levamisole, linomide, LM609, matrix metalloproteinase inhibitor, marimastat (BB-2516), medroxyprogesterone, 6-methylmercaptopurine riboside, metastat (Col-3), methotrexate, minocycline, nitric oxide, octreotide (somatostatin analogue), Paclitaxel, D-penicillamine, pentosan polysulfate, placental proliferin-related protein, placental RNase inhibitor, plasminogen activator inhibitor (PAIs), platelet factor-4, prednisolone, prolactin (16-Kda fragment), proliferin-related protein, prostaglandin synthase inhibitor, protamine, retinoids, Roquinimex (LS-2616, linomide), somatostatin, stromelysin inhibitor, substance P, suramin, SU101, tecogalan sodium (DS-4152), tetrahydrocortisolsthrombospon dins (TSPs), tissue inhibitor of metalloproteinases (TIMP 1, 2, 3), vascular endothelial growth factor inhibitors, vitamin A , Vitaxin and vitreous fluids.

The antineoplasm agent is an alkylating agent, an antimetabolite, a natural product, a platinum coordination complex, an anthracenedione, a substituted urea, a methylhydrazine derivative, an adrenocortical suppressant, a hormone, an antagonist, an anti-cancer polysaccharide, and an anti-cancer herb extract. The neoplasm is an oncogene inhibitor or a tumor suppressor gene or protein, where the oncogene inhibitor is an anti-oncogene antibody or an anti-oncogene antisense oligonucleotide. The oncogene is selected from abl, erbA, erbB, ets, fes (fps), fgr, fms, fos, hst, int1, int2, jun, hit, B-lym, mas, met, mil, (raf), mos, myb, myc, N-myc, neu (ErbB2), ral (mil), Ha-ras, Ki-ras, N-ras, rel, ros, sis, src, ski, trk, and yes.

The tumor suppressor gene may consist of p16, p21, p27, p53, RB, WT-1, DCC, NF-1 or APC. The combination may further comprise a viral vector carrying an oncogene or a tumor suppressor gene sequence. The viral vector is an adenovirus vector, a simian virus vector, a conditionally replicating human immunodeficiency viral vector, a retrovirus vector, an SV40 vector, a Herpes simplex viral amplicon vector, or a Vaccinia virus vector. The combination also comprises a facilitating agent that facilitates conjugation between the hapten and a tumor antigen. The facilitating agent is a chelator or a chemical linking agent, specifically a glycyltyrosyl-N(N-e-diethylenetri-aminepetaacetic acid)-lysine (GYK-DTPA) or doxorubicin adipicdihydrazide (ADR-ADH).

The chemical linking agent is carbodiimide. The combination further includes an immune response potentiator, selected from Bacille Calmette-Guerin, Corynebacterium Parvum, Brucella abortus extract, glucan, levamisole, tilogone, an enzyme and a non-virulent virus. The enzyme is selected from Vibrio cholera neuraminidase (VCN), Papa in, beta-Gal and Con A. The non-virulent virus is a non-virulent Newcastle virus. The combination may also comprise a coagulation lyzing agent, such as proteinase K, Glycosyl-phosphatidylinositol-B7, or pancreatin.

The combination preferably has H2O2 as oxidizing agent, ethanol as protein denaturing agent, the hapten is TNP, and the facilitating agent is carbodiimide. The oxidizing or reducing agent is about 0.01-35% (w/w), the protein denaturing agent is 1-99% (w/w), and the hapten is 1-80 mg/ml.

Preferred Method: The mammal is a human. The method also comprises administering to neoplasm a facilitating agent that facilitates conjugation between the hapten and tumor antigen of the neoplasm, where the facilitating agent is a chelator or a chemical linking agent. The method also includes administering an immune response potentiator to the neoplasm, and a coagulation- lyzing agent, which comprises an oxidizing agent or a reducing agent, and a protein-denaturing agent. The oxidizing agent is selected from hydrogen peroxide (H2O2), ozone, polyatomic oxygen O7, polyatomic oxygen O8, NaIO4, potassium peroxymonosulfate (oxone), D,L-S-methyllipoic acid methyl ester, tertiary butyl hydroperoxide, menadione, diamide, iodogen, N-bromosuccinimide, omeprazole, and N-ethylmaleimide.

The reducing agent is a hematoxylin, a hypoxic reducing agent, or non-nitro compound SR 4233, where the reducing agent is a nitroimidazole. The protein-denaturing agent is selected from alcohol, guanidine hydrochloride, guanidinium thiocyanate, sodium citrate, 2-mercaptoethanol, sarcosyl, phenol, chloroform and urea. The coagulation treatment is selected from cryotherapy, laser coagulation (ILC), percutaneous microwave coagulation therapy, radio-frequency-induced coagulation necrosis, transpupillary thermotherapy, ultrasonic therapy, and radiation therapy.

The autologous immune response generated by the combined action of the hapten and the coagulation agent or treatment comprises or is a humoral and/or cellular immune response. Neoplasms which can be treated include adrenal gland, anus, auditory nerve, bile ducts, bladder, bone, brain, breast, bruccal, central nervous system, cervix, colon, ear, endometrium, esophagus, eye, eyelids, fallopian tube, gastrointestinal tract, head and neck, heart, kidney, larynx, liver, lung, mandible, mandibular condyle, maxilla, mouth, nasopharynx, nose, oral cavity, ovary, pancreas, parotid gland, penis, pinna, pituitary, prostate gland, rectum, retina,

salivary glands, skin, small intestine, spinal cord, stomach, testes, thyroid, tonsil, urethra, uterus, vagina , bestibulocochlear nerve, and vulva neoplasm.
The neoplasm to be treated is a solid tumor, larger than 108 cells, or about 5x109-1011 cells. The hapten and coagulation agents are administered via injection, or through a surgical procedure.
The method further comprises administering in situ, a molecule is selected from suicide gene sequence, a cytolytic gene sequence, a cytokine gene sequence, a radiation sensitizer, a cytokine-containing depot, a reporter and a reporter gene sequence.

L119 ANSWER 5 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2001-488831 [53] WPIX
DNC C2001-146786
TI Treating patient who has failed immunostimulatory treatment attempt for treating superficial bladder cancer by introducing Mycobacterium, and **interferon** alpha, beta or **gamma** or interleukin (IL)-1-3, IL-12, IL-15 or IL-18.
DC B04 D16
IN O'DONNELL, M A
PA (ODON-I) O'DONNELL M A
CYC 24
PI WO 2001056387 A1 20010809 (200153)* EN 99p A01N063-00
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AU CA JP US
AU 2001033076 A 20010814 (200173) A01N063-00
ADT WO 2001056387 A1 WO 2001-US2827 20010129; AU 2001033076 A AU 2001-33076 20010129
FDT AU 2001033076 A Based on WO 200156387
PRAI US 2000-495100 20000201
IC ICM A01N063-00
ICS A01N065-00
AB WO 200156387 A UPAB: 20010919
NOVELTY - Immunotherapeutically treating patients affected with superficial bladder cancer, where the patient has failed an immunostimulatory therapeutic treatment (a cytokine-included treatment) attempt previously, involves introducing viable Mycobacterium species, and concurrently introducing cytokine such as **interferon** alpha , beta or **gamma** , interleukin (IL)-1-3, IL-12, IL-15 or IL-18.
DETAILED DESCRIPTION - Immunotherapeutically treating patient affected with superficial bladder cancer, where the patient has failed immunostimulatory therapeutic treatment (a cytokine-included treatment) attempt previously, involves (M1) initiating the following treatment processes of:
(i) introducing at least one viable Mycobacterium species into the bladder of the patient where the Mycobacterium species is a recombinant DNA mycobacterial strain, a substantially non-pathogenic Mycobacterium species, or M. bovis-Bacillus Calmette-Guerin (BCG); and
(ii) causing a concurrently introduction of a cytokine in the bladder of the patient, where the cytokine is any type of isoform of **IFN** - alpha , beta or **gamma** , IL-1, IL-2, IL-3, IL-12, IL-15 or IL-18 and then allowing the Mycobacterium species and cytokine to act in combination in the bladder for a preset period of time.
INDEPENDENT CLAIMS are also included for the following:
(1) immunotherapeutically treating patient affected with upper urinary tract cancer choosing an anatomic site in the upper urinary tract for immunotreatment and introducing the viable Mycobacterium species as described above and causing a concurrent introduction of a cytokine as described above at the chosen anatomic site in the upper urinary tract of the patient, and allowing the Mycobacterium species and the cytokine to act in combination at the chosen anatomic site in the upper urinary tract as an immunotherapeutic treatment for a preset period of time; and
(2) primary immunotherapeutic method for treating a patient afflicted

with a form of urinary cancer, where the patient has not received any immunostimulatory agents previously as a cancer treatment regimen, method involves introducing the viable Mycobacterium species as described above and causing a concurrent introduction of not less than two cytokines as described above at the chosen anatomic site in the body of the patient and then allowing the Mycobacterium species and the two different cytokines to act in combination at the chosen anatomic site in the body as an immunotherapeutic treatment for a preset period of time.

ACTIVITY - Cytostatic; antitumor.

Prior cytokine failure human patients (Group Ia) were tested with 6 weeks of 1/10th standard dose BCG plus 100 MU of **interferon** (**IFN**)-a-2B. Patients failing a prior induction cycle of combination BCG plus a cytokine (Group Ib) may receive a 2nd induction cycle. Patients with upper tract transitional cell carcinoma regardless of prior therapy would also be treated with the same regimen (Group Ic).

If treatment intolerance occurs in any group during the induction period, the patient was optionally given a 2-week rest followed by re-initiation of treatments at a BCG dose of roughly 1/3 that of the prior dose. Similar 2-week delays were permitted for repeat episodes of intolerance. Intravesical therapy was delivered via a temporarily placed foley catheter for a total of 6 induction treatments for patients with bladder transitional cell carcinoma (TCC). For those with upper tract TCC, a small (usually 4 French) temporary external stent was placed cystoscopically from the bladder into the mid renal pelvis when possible.

Standard cystoscopic and cytological evaluations were performed at roughly 3-month intervals during the first 2 years although 6-month intervals may be appropriate during the second year for patients with less aggressive disease. Combination of **low-dose** BCG plus **IFN**- alpha showed great success in patients with upper tract TCC. Five of 5 patients with a total of 7 upper tracts affected by carcinoma in-situ (CIS) manifested by positive cytologies had complete responses to therapy with ongoing remissions at (23+, 20+), 13+, (11+, 6+), 6+ and 5+ months, respectively. And the patient with recurrent low-grade papillary TCC despite laser ablation was disease free after 2 courses of reduced BCG plus **IFN**- alpha .

MECHANISM OF ACTION - Immune response stimulator; induces bladder cytokine milieu which phenotypically alters cancer cells to become better immune targets; recruitment and activation of effector cells into bladder to kill immunotargets appropriate.

USE - For treating persons afflicted with superficial bladder cancers who have failed an immunostimulatory therapeutic treatment attempt previously and for treating patients who have not undergone any such immunostimulatory therapeutic treatment regimen for cancer and also for treating patients afflicted with upper urinary tract (ureters and renal pelvic region) cancers (claimed).

The method is specifically useful for treating different tumors and neoplasms formed in the ureter and renal pelvis regions, and various tumors and neoplasms constituting superficial bladder cancers.

ADVANTAGE - The method allows for treating bladder cancer patients who have undergone one or more treatment attempts unsuccessfully and presently have no medical recourse or course of treatment alternatives. The method provides effective control and upper tract and superficial bladder cancer patients. The therapeutic regimen results in remission of the disease in upper urinary tract and eventually leads to a disease free state in the ureter and renal pelvis areas.

Dwg.0/22

FS CPI

FA AB; DCN

MC CPI: B04-B04C1; B04-B04C2; B04-B04D2; B04-C01; B04-F10B2; B04-G05; B04-G07; B04-H0200E; B04-H05; B04-N02; B04-P01; B11-A01; B11-C07A; B11-C08E1; B12-M05; B14-G01; B14-G03; **B14-H01**; B14-N07; B14-S11; D05-H04; D05-H07; D05-H08; D05-H11

TECH UPTX: 20010919

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The cytokines are introduced concurrently and multiple treatment occasions are given to the patients. Preferably, in all the above mentioned methods, the Mycobacterium species is present in combination with the blend of 3-9 different cytokines.

L119 ANSWER 6 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2001-451850 [48] WPIX
DNC C2001-136519
TI Novel monocyte derived-dendritic cells, which do not express CD1a marker, lack interleukin-12 production, produce IL-10, promote Th0/Th2 lineage differentiation of T cells, used for inducing immune response in humans.
DC B04 D16
IN CHANG, C J; PUNNONEN, J
PA (CHAN-I) CHANG C J; (PUNN-I) PUNNONEN J; (MAXY-N) MAXYGEN INC
CYC 94
PI WO 2001051617 A1 20010719 (200148)* EN 83p C12N005-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2001026937 A1 20011004 (200161) A61K048-00
AU 2001032793 A 20010724 (200166) C12N005-06
ADT WO 2001051617 A1 WO 2001-US1162 20010110; US 2001026937 A1 Provisional US 2000-175552P 20000111, Provisional US 2000-181957P 20000210, US 2001-760388 20010110; AU 2001032793 A AU 2001-32793 20010110
FDT AU 2001032793 A Based on WO 200151617
PRAI US 2000-181957P 20000210; US 2000-175552P 20000111; US 2001-760388 20010110
IC ICM A61K048-00; C12N005-06
ICS A01N063-00; A61K039-385; C12N005-00; C12N005-02
AB WO 200151617 A UPAB: 20010829
NOVELTY - A monocyte derived-dendritic cell (DC) (I), which does not express a CD1a cell marker, substantially lacks interleukin (IL)-12 production, produces IL-10 and promotes Th0/Th2 lineage differentiation of T cells, is new.

DETAILED DESCRIPTION - A monocyte derived-dendritic cell (DC) (I), which does not express a CD1a cell marker, substantially lacks interleukin (IL)-12 production, produces IL-10 and promotes Th0/Th2 lineage differentiation of T cells, is new.

(I) is produced by culturing a population of monocytes in IL-4, granulocyte macrophage colony stimulating factor (GM-CSF), and a culture medium comprising insulin, transferrin, linoleic acid, oleic acid and palmitic acid.

(I) does not express a CD1a cell marker, substantially lacks interleukin (IL)-12 production, produces IL-10 and promotes Th0/Th2 lineage differentiation of T cells. (I) has an altered cytokine profile compared to a DC produced by culturing a population of monocyte cells in a IL-4, GM-CSF and a culture medium comprising RPMI.

INDEPENDENT CLAIMS are also included for the following:

(1) producing (M1) a differentiated antigen presenting cell (APC), involves culturing a population of peripheral blood or bone marrow mononuclear cells in IL-4, GM-CSF, and a culture medium comprising insulin, transferrin, linoleic acid, oleic acid, palmitic acid for a sufficient time to produce the differentiated APC;

(2) a differentiated APC, which does not express a CD1a cell marker;

(3) a differentiated T cell produced by coculturing the population of T cells with a population of (I);

(4) a composition comprising (I);

(5) a method (M2) for inducing differentiation of naive T cells which involves coculturing a population of T cells with population of CD1a- APC

(CD1a- DC, i.e., (I)), thus inducing or promoting differentiation of the T cells;

(6) an ex vivo method for inducing a therapeutic or prophylactic immune response against an antigen which involves culturing a population of monocytes obtained from the subject with IL-4, GM-CSF and a culture medium comprising Iscove's modified Dulbecco's medium (IMDM) (preferably Yssel's medium) supplemented with insulin, transferrin, linoleic acid, oleic acid and palmitic acid to produce a population of DC comprising CD1a- DC, introducing to the population of CD1a- DC, an antigen or a sufficient amount of exogenous DNA operably linked to a promoter that controls expression of the DNA sequence, that encodes an antigen, such that the presentation of the antigen on the CD1a- DC results and administering the antigen presenting CD1a- DC to the subject to induce a therapeutic or prophylactic immune response against the antigen;

(7) a method for therapeutic or prophylactically treating a disease in a subject suffering from the disease, comprising introducing to the population of CD1a- DC produced from monocytes obtained from the subject, as described above, a disease associated antigen or a sufficient amount of exogenous DNA operably linked to a promoter that controls expression of the DNA sequence that encodes disease-associated antigen, such that the presentation of the antigen on the CD1a- DC results and administering the therapeutic or prophylactic amount of CD1a- DC presenting the diseases associated antigen, to treat the disease; and

(8) a method for therapeutically or prophylactically treating a disease such as cancer in a subject which involves culturing a population of monocytes obtained from a subject as described above, to produce a population of CD1a- DC, contacting the population of CD1a- DC with the population of diseased cells from a tissue or organ of the subject, thus inducing presentation of the disease associated antigen on the CD1a- DC and administering the therapeutic or prophylactic amount of CD1a- DC to the subject.

ACTIVITY - Cytostatic; antirheumatic; antiarthritic; antiinflammatory; dermatalogical; immunosuppressive; virucide; antibacterial; antimalarial; tuberculostatic; antileprotic; antiallergic; neuroprotective; antidiabetic; antipsoriatic.

MECHANISM OF ACTION - Adjuvant; immune responses modulator; vaccine; differentiation of T cells to Th0/Th2 subtype promoter; ex vivo gene therapy.

USE - (I) is useful for inducing an immune response in a in a human or nonhuman animal to at least one antigen. (I) is also useful for inducing differentiation of naive T cells which involves coculturing a population of T cells with population of CD1a- APC. (I) is also useful for modulating an immune response in an immunocompromised subject by inducing or modulating immune response in the subject. (I) is also useful ex vivo for inducing a therapeutic or prophylactic immune response against an antigen. (I) is also useful for a method for therapeutically or prophylactically treating a disease such as cancer in a subject (claimed).

(I) is useful as antigen presenting cells in methods for therapeutic and prophylactic treatment of diseases and disorders, genetic vaccine or protein vaccine applications, immunotherapies and gene therapy. (I) is useful for in vitro, in vivo and ex vivo therapeutic applications by modulating immune responses in conditions such as rheumatoid arthritis, lupus erythematosis, and transplant rejection and thus useful for ameliorating symptoms and progression of such disease states. (I) is also useful for activating T cells recognizing antigens of interest. (I) is also useful to induce a prophylactic immune response, serving as vaccine for antigens that activate a T cell response or T dependent antibody response. Dendritic cell vaccines comprising monocyte derived APC or (I) is useful for treating cancers such as leukemia, melanoma, prostate cancer, pancreatic cancer, etc. (I) is useful for vaccination against viral diseases and disorders e.g., hepatitis B and C virus, herpes simplex virus, Epstein-Barr virus, human immunodeficiency virus, etc.,; diseases and disorders relating to bacterial, mycobacterial (TB, leprosy, etc.,),

allergies, malaria, autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile diabetes, psoriasis, etc.,; parasitic, inflammatory, infectious, hyperproliferative, contraception, etc. (I) is also useful as an adjuvant for enhancing an immune response to an antigen.

ADVANTAGE - (I) has a higher transfection efficiency than that of a DC produced by culturing a population of monocytes in IL-4 and GM-CSF and a culture medium comprising RPMI (claimed). (I) has increased potency as adjuvant since small members of mDC2 pulsed with **low doses** of antigen stimulate a stronger T cell response; primary response e.g., naive and quiescent T cells can be activated with antigens on mDC2; and also CD4+ helpers and CD8+ killers can be primed in vivo and ex vivo.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-B04C2; B04-E03F; B04-F02; B04-F0200E; B04-F04; B11-C08; B12-K04A; **B14-A01**; B14-A02; B14-A03B; B14-B02; B14-C09B; B14-G01; B14-G02; B14-G03; **B14-H01**; B14-N07A; B14-N12; B14-N13; B14-N17; B14-P02; B14-S01; B14-S03; B14-S04; B14-S11; B14-S12; D05-H08; D05-H09; D05-H12A; D05-H14B2

TECH UPTX: 20010829

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M1), a differentiated APC such as a DC is produced. Preferably, the DC produced is a CD1a- DC, referred to as mDC2, which has increased IL-10 production as compared to a DC produced by culturing a population of peripheral blood or mononuclear cells in IL-4, GM-CSF and a culture medium comprising RPMI; substantially lacks IL-12 production, and is capable of presenting an antigen to a T cell. Preferably, the DC produced induces or promotes Th0/Th2 differentiation of T cells. For the production of differentiated APC described above, the population of mononuclear cells (comprising monocytes) is derived from a human or a nonhuman animal and depleting the population of mononuclear cells of T, B, natural killer (NK) cells with immunomagnetic beads. Alternately, the population of mononuclear cells is derived by density gradient separation of standard buffy coat preparation of peripheral blood which are also depleted of the population of mononuclear cells as described above. The process is carried out using a culture medium that comprises Iscove's modified Dulbecco's medium (IMDM) supplemented with insulin, transferrin, linoleic acid, oleic acid and palmitic acid, 0.25% (w/v) bovine serum albumin, and 1.5-2 mg/l 2-amino ethanol. Alternately, the culture medium comprises Yssel's medium comprising 10% fetal bovine serum (FBS), 2 mM glutamine, 50 units (U)/ml and about 100 micrograms/ml of streptomycin.

After producing DC using Yssel's medium, the method further involves culturing the APC in the presence of anti-CD40 monoclonal antibody for a period of approximately 24 hours, thereby producing an activated APC, culturing the activated APC in the presence of lipopolysaccharide (LPS) and **interferon (IFN)-gamma** for a period of approximately 48 hours, therefore producing a matured CD83+, CD1a- DC.

(M1) further involves introducing to at least one CD1a- DC an exogenous DNA sequence operably linked to a promoter that is capable of controlling expression of the DNA sequence, which encodes at least one antigen, such that expression and the presentation of the antigen results, thus producing an antigen presenting CD1a- DC. The exogenous DNA sequence is introduced into the DC by electroporation, injection, microinjection, gene gun delivery, lipofection, DOTAP supplemented lipofection, DOSPER supplemented lipofection, or superfection.

Alternatively, (M1) involves introducing a sufficient amount of antigen or its fragment to the DC such that presentation of the at least one antigen on at least one CD1a- DC occurs, thus producing an antigen presenting CD1a- DC.

In M2, the CD1a- APC is (I).

Preferred Cell: A differentiated APC that does express CD1a cell surface marker is preferably (I) (mDC2) as described above.

Preferred Composition: The composition comprising CD1a- DC which display or present an antigen or its fragment e.g., of a protein or peptide differentially expressed on a tumor cell, bacterially infected cell, a parasitically infected cell, or a virally infected cell or a target cell of an autoimmune response. The composition is preferably a vaccine comprising a carrier.

L119 ANSWER 7 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2001-355454 [37] WPIX
DNC C2001-110167
TI **Low-dosage interferon gamma** (**IFN-gamma**) or a combination of **low-dosage IFN-gamma** with glucocorticoids, used for the manufacture of a medicament or a combination of medicaments for the long-term treatment of bronchial asthma.
DC B04
IN BLOCK, L; ZIESCHE, R
PA (BLOC-I) BLOCK L
CYC 91
PI WO 2001034180 A2 20010517 (200137)* EN 15p A61K038-21 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001013923 A 20010606 (200152) A61K038-21 <--
ADT WO 2001034180 A2 WO 2000-EP10941 20001106; AU 2001013923 A AU 2001-13923 20001106
FDT AU 2001013923 A Based on WO 200134180
PRAI EP 1999-122357 19991110
IC ICM **A61K038-21**
ICS A61K031-573; A61P011-06
ICI **A61K038-21**; A61K031:573
AB WO 200134180 A UPAB: 20010704
NOVELTY - Use of **low-dosage interferon gamma** (**IFN- gamma**) or a combination of **low-dosage IFN- gamma** with glucocorticoids for the manufacture of a medicament or a combination of medicaments for the long-term treatment of bronchial asthma.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) use of **IFN- gamma** or a combination of **IFN- gamma** with a glucocorticoid for the manufacture of a medicament for the prophylactic prevention of redevelopment and continuous growth of nasal polyps after surgical removal associated to asthma or disorders which are based on similar inflammatory processes;
(2) use of **low-dosage IFN-gamma** or a combination of **low-dosage IFN- gamma** with a glucocorticoid for the manufacture of a medicament for reducing increased expression of the inflammation mediators interleukin (IL)-13 and transforming growth factor (TGF)- beta 1 in the bronchial mucosa tissue of asthma patients;
(3) use of **IFN- gamma** or a combination of **IFN- gamma** with a glucocorticoid for the manufacture of a medicament for the treatment of individuals having an increased level of IL-13 and TGF- beta 1 in their bronchial mucosa tissue;
(4) a method for a long-term treatment of bronchial asthma in a patient comprising administering **IFN- gamma** in **low doses** or a combination of **low-dosage IFN- gamma** with a glucocorticoid, where the period of administration varies from 4-24 months;
(5) a method for a long-term treatment of bronchial asthma in a patient comprising administering **low-dosage**

IFN- gamma or a combination of **low-dosage** of **IFN- gamma** a with a glucocorticoid, where a single dose of 5-100 micro g **IFN- gamma** is administered 1-5 times per week;

(6) a method for a long-term treatment of bronchial asthma in a patient comprising administering **low-dosage IFN- gamma** , where a single dose of 5-100 micro - **gamma** is administered 1-5 times per week for a period of 4-24 months;

(7) a method for a long-term treatment of bronchial asthma in a patient comprising administering **low-dosage IFN- gamma** , where the weekly over-all dose of **IFN- gamma** administered to the patient does not exceed 300 micro g and the period of administration varies from 4-24 months;

(8) a method for preventing redevelopment and continuous growths after surgical removal of nasal polyps associated to asthma and disorders which are based on similar inflammatory processes, comprising administering to a patient **IFN- gamma** or a combination of **IFN- gamma** with a glucocorticoid;

(9) method for reducing increased expression of the inflammation mediators IL-13 and TGF- beta 1 in bronchial mucosa tissue of asthma patients comprising administering **low-dosage IFN- gamma** or a combination of **low-dosage IFN- gamma** with a glucocorticoid; and

(10) a method for treating individuals having increased levels of the inflammation mediators IL-13 and TGF- beta 1 in their bronchial mucosa tissue comprising administering **IFN- gamma** or a combination of **IFN- gamma** with a glucocorticoid.

ACTIVITY - Antiasthmatic; antiinflammatory.

MECHANISM OF ACTION - None given.

USE - **Interferon gamma** is useful for the treatment of asthma.

ADVANTAGE - Long term treatment of severe asthma bronchiale.

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B01-B02; **B04-H05C**; **B14-C03**; **B14-K01A**
TECH UPTX: 20010704

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Features: The bronchial asthma is resistant or essentially resistant against glucaeorticoid treatment, if the glucocorticoid is administered alone. The bronchial asthma is accompanied by nasal polyposis. The glucocorticoid is prednisolone.

L119 ANSWER 8 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2001-061658 [07] WPIX
DNC C2001-017158
TI Novel product comprising proliferatively active moiety linked to genetic material, useful as vectors for protected nucleic acid material and as mitogen to stimulate proliferation of target cell.
DC A96 B04 D16
IN DELLA, B R; FRANKS, C R; KNIGHT, D J; MAITLAND, N J; DELLA BITTA, R
PA (BIOI-N) BIO INNOVATION LTD
CYC 94
PI WO 2000074724 A2 20001214 (200107)* EN 49p A61K048-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000050886 A 20001228 (200119) A61K048-00
EP 1185304 A2 20020313 (200225) EN A61K048-00

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SI

ADT WO 2000074724 A2 WO 2000-GB2014 20000605; AU 2000050886 A AU 2000-50886 20000605; EP 1185304 A2 EP 2000-935338 20000605, WO 2000-GB2014 20000605

FDT AU 2000050886 A Based on WO 200074724; EP 1185304 A2 Based on WO 200074724

PRAI US 1999-137592P 19990603; GB 1999-12807 19990603

IC ICM A61K048-00

AB WO 200074724 A UPAB: 20011129

NOVELTY - A product (I) comprising a proliferatively active moiety (PAM) linked to genetic or nucleic acid material which is associated with a protective material (PM), is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a pharmaceutical formulation (II) comprising (I).

ACTIVITY - Immunosuppressive; antiviral; cytostatic.

No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - (I) is useful for manufacturing a medicament for treating e.g. an autoimmune disease, transplant rejection, retroviral disease, graft-versus-host-disease, or lymphoproliferative disease, comprising cells bearing a high affinity receptor for PAM. (I) is also useful for treating the diseases. (I) is useful for manufacturing medicament for internalizing the biological active agent into the cell having a high affinity receptor for PAM, cytokine or growth factor of (I), and optionally for stimulating lymphocyte proliferation. (All claimed). (I) is also useful in gene therapy as a vector for protected nucleic acid material, and as a mitogen to stimulate proliferation of target cells. (I) having epidermal growth factor (EGF) receptor binding function is useful for targeting anticancer drugs to most tumor types.

ADVANTAGE - The product can be administered at exceedingly **low doses** so that little or no systemic toxicity results. The growth factor/cytokine stimulates the target system and the nucleic acid moiety induces the therapeutic effect. The biodistribution of the product is predictable and good. The product has very low immunogenicity and effective targeting capacity.

Dwg.0/9

FS CPI

FA AB; DCN

MC CPI: A12-V01; A12-W11L; B04-E01; B04-E08; B04-H02B; B04-H02C; B04-H02F; B04-H02G; B04-H04; B04-H05; B04-H06; B04-H07; B04-H16; B14-A02B1; B14-F02E; B14-G02C; B14-G02D; **B14-H01**; B14-S03; D05-H12E

TECH UPTX: 20010202

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Product: (I) comprises a PM comprising a micelle-forming or complex-forming material. The complex-forming material comprises polylysine, and the micelle-forming material comprises phospholipids. The genetic material comprises an expression vector containing a gene encoding a protein, operably linked to a control sequence, or a plasmid construct. The gene is a cytotoxic gene, a defect correction gene or an immunogene. The cytotoxic gene is for expressing an enzyme such as thymidine kinase, cytosine deaminase, cytochrome P-450 or bacterial nitroreductase, to convert a prodrug into a toxic drug. The control sequence comprises a cytomegalovirus (CMV) promoter. The genetic material contains an episomal maintenance sequence, and two or more genes, the second and any subsequent genes are operably linked to an internal ribosomal entry site. The nucleic acid material comprises an anti-sense sequence. The link between the agent and the moiety is intracellularly cleavable by acid hydrolysis. The target cells of PAM such as cytokine or growth factor, have high affinity receptor. The cytokine is interleukin (IL)-2 or IL-6, tumor necrosis factor (TNF)alpha, macrophage-colony stimulating factor (M-CSF), **interferons** (IFN)alpha, IFNbeta or **IFNgamma**, fibroblast growth factor (FGF), insulin-like growth factor (IGF), transforming growth factor (TGF)beta, granulocyte monocyte (GM)-CSF, stem cell factor (SCF), granulocyte (G)-CSF or an Erythropoietin (Epo). PAM is a growth factor molecule such as Epo,

GM-CSF, G-CSF, SCF, Multi-CSF (IL-3), M-CSF, epidermal (E)-CSF (IL-5), IGF-1, Platelet-derived growth factor (PDGF), or TGFbeta2. The moiety is a recombinant human cytokine optionally modified by amino acid alterations. The recombinant IL-2 is desala1-IL-2 SER125. (I) further comprises a biologically active material such as genetic material or antisense nucleotide sequences, and PM linked to cytokine growth factor having target cells capable of presenting a high affinity receptor. The nucleotide attached to the proliferated active moiety is linked with the cationic DNA binding material such as polymer, liposome or dendrimer. The DNA binding material is a polymer comprising polylysine, its derivative or polyethyleneimine. The DNA binding material forms a bridge between active moiety and the nucleotide, or forms a complex with the nucleotide. (I) further comprises a first domain comprising an IL-2 sequence functionally recognized by high affinity IL-2 receptor to promote proliferation, linked to the second domain comprising a gene for functional Adenosine deaminase activity (ADA), optionally associated with PM. (I) comprises a functional IL-2 linked to an expression vector comprising a gene for functional ADA. PAM is linked to encapsulated or complex nucleic acid material. (I) comprises a moiety having M-CSF, SCF or GM-CSF function linked to a functional acid sphingomyelinase gene.

L119 ANSWER 9 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2000-412215 [35] WPIX
DNN N2000-308126 DNC C2000-124972
TI Use of interferon-alpha for enhancing expression of an aquaporin protein in aquaporin producing cells of a warm-blooded vertebrate having diminished tear production, abnormal mouth dryness and cystic fibrosis.
DC B04 C03 P72
IN **CUMMINS, J M**; SMITH, K J; SMITH, J K
PA (AMAR-N) AMARILLO BIOSCIENCES INC; (UYET-N) UNIV EAST TENNESSEE STATE; (CUMM-I) CUMMINS J M; (SMIT-I) SMITH J K
CYC 91
PI WO 2000032387 A1 20000608 (200035)* EN 24p B31F001-10
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000020318 A 20000619 (200044) B31F001-10
EP 1147011 A1 20011024 (200171) EN B31F001-10
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 2002037273 A1 20020328 (200225) A61K038-21 <--
ADT WO 2000032387 A1 WO 1999-US28045 19991124; AU 2000020318 A AU 2000-20318 19991124; EP 1147011 A1 EP 1999-963991 19991124, WO 1999-US28045 19991124; US 2002037273 A1 Provisional US 1998-109791P 19981125, Div ex US 1999-448698 19991124, US 2001-964792 20010927
FDT AU 2000020318 A Based on WO 200032387; EP 1147011 A1 Based on WO 200032387
PRAI US 1998-109791P 19981125; US 1999-448698 19991124; US 2001-964792 20010927
IC ICM **A61K038-21**; B31F001-10
ICS C07C059-90
AB WO 200032387 A UPAB: 20000725
NOVELTY - Enhancing expression of an aquaporin protein (II) in aquaporin producing cells (III) of a warm-blooded vertebrate, comprising contacting the cells with interferon (IFN)- alpha to upregulate aquaporin expression in them, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) enhancing saliva production in a patient having a disease causing a dry mouth, comprising administering IFN- alpha in a saliva soluble or miscible form, and holding the IFN- alpha in the mouth to contact the oral mucosa, which includes saliva-producing cells;

(2) enhancing lacrimation in a warm-blooded vertebrate having a disease characterized by attenuated function of lacrimating cells, comprising administering IFN- alpha ; and

(3) improving pulmonary function in a patient having a pulmonary disorder characterized by blocked airways, comprising administering IFN-alpha , to upregulate (II) expression in lung cells, and enhance mucous mobilization.

ACTIVITY - Anti-xerotic.

MECHANISM OF ACTION - Up regulation of aquaporin; water homeostasis enhancer. The biological activity of IFN- alpha in increasing aquaporin production for increasing saliva production in was tested in 9 human immunodeficiency virus (HIV) patients suffering from xerostomia. IFN-alpha was diluted and compressed into lozenges. Three 150 IU lozenges were administered to the subjects 3 times/day and the treatment was continued for a total of 12 weeks. The assessments made were based upon changes in salivary flow rates, oral dryness as reported by the subjects. Changes in unstimulated whole saliva or stimulated whole saliva were studied. 3 of the 9 subjects had a positive response for whole saliva and unstimulated whole saliva. 6 of 8 patients had a clinically significant increase in visual analog scale for oral dryness.

USE - IFN- alpha is used for up regulating aquaporin protein expression in cells exhibiting abnormal dryness is helpful in treating a patient afflicted with the condition causing xerosis, in which the disease condition is alleviated by enhancing the cells ability to release water. Enhanced production of (II) is useful for enhancing saliva production in a patient affected with the disease state producing mouth dryness (xerostomia), for enhancing lacrimation in a warm-blooded vertebrate having a disease state characterized by attenuated function of cells responsible for lacrimation, and for improving pulmonary function in a patient suffering from a pulmonary disorder characterized by mucous blocked airways (claimed). IFN- alpha is also used for treating a patient with cystic fibrosis, or afflicted with abnormal vaginal dryness, and for treating keratoconjunctivitis sicca in dogs.

Dwg.0/3

FS CPI GMPI
FA AB; DCN
MC CPI: B04-B04G; B04-F02; B04-H05A; B04-K01; B04-N04; B14-N07; B14-S12; C04-B04G; C04-F02; C04-H05A; C04-K01; C04-N04; C14-N07; C14-S12
TECH UPTX: 20000725

TECHNOLOGY FOCUS - BIOLOGY - Preferred Cells: (III) forms a part of vertebrate tissue such as oral mucosa, nasopharyngeal mucosa and adjacent salivary glands, conjunctiva or lacrimal gland, lungs or vaginal tissue.

L119 ANSWER 10 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 2000-128221 [12] WPIX
DNC C2000-039348
TI Novel agent used to treat human T-cell lymphotropic virus-1 related diseases.
DC A96 B04 D16
IN KURIMOTO, M; OHASHI, K
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU
CYC 28
PI EP 974358 A2 20000126 (200012)* EN 13p A61K038-21 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2000095703 A 20000404 (200027) 8p A61K038-21 <--
KR 2000011960 A 20000225 (200102) A61K038-21 <--
US 6299871 B1 20011009 (200162) A61K037-66
US 2002039570 A1 20020404 (200227) A61K038-21 <--
ADT EP 974358 A2 EP 1999-305815 19990722; JP 2000095703 A JP 1999-210030 19990726; KR 2000011960 A KR 1999-30218 19990724; US 6299871 B1 US 1999-357913 19990721; US 2002039570 A1 Cont of US 1999-357913 19990721, US 2001-969866 20011004

FDT US 2002039570 A1 Cont of US 6299871
PRAI JP 1998-209294 19980724
IC ICM A61K037-66; **A61K038-21**
ICS A61K009-16; A61K009-20; A61K009-28; A61K031-00; **A61K038-00**; A61K045-00; C12N005-06; C12N005-16; C12P021-04; C12Q001-70
AB EP 974358 A UPAB: 20000308
NOVELTY - An orally-administerable therapeutic and/or prophylactic agent (I) for human T-cell lymphotropic virus (HTLV)1-related disease, comprising an **interferon- gamma** as an effective ingredient and a pharmaceutically acceptable carrier, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the use of **interferon- gamma** for the manufacture of (I).

ACTIVITY - Cytostatic; immunosuppressive; antiarthritic; antirheumatic; dermatological; anti-inflammatory; ophthalmological; virucide.

Three patients with adult T-cell leukemia, were orally administered with 200 mg/tablet of the agent, containing 1000 units of **interferon- gamma** , three times a day for six months. Two patients were administered for the same period a 200 mg/tablet placebo consisting of a base of the novel agent but lacking any **interferon - gamma** . In the control patients the HTLV-1 virus levels in the blood remained close to 100% over the six months, in two of the treated patients the level dropped to 0.1 and 0.01% respectively, the third treated patient had viral levels which remained close to 100%.

MECHANISM OF ACTION - None given.

USE - The agent is used to treat human T-cell lymphotropic virus-1 related diseases, especially adult T-cell leukemia, Sjogren syndrome, chronic rheumatoid arthritis, systemic lupus erythematosus, uveitis, and immunopathies (claimed).

ADVANTAGE - The novel agent allows oral administration of the **interferon- gamma** , rather than having to use intramuscular injection, which greatly reduces the dosage which needs to be administered, resulting in fewer side effects, such as serious depression of liver function, leukopenia, neutropenia, calcium lowering and fervescence, and reduced costs.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: A03-A00A; A03-C01; A12-V01; **B04-H05C**; B14-A02; **B14-C03**; B14-C06; B14-C09B; B14-G02; **B14-H01**; B14-H01A; B14-N03; B14-N17; D05-H17A2
TECH UPTX: 20000308
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred agent: (I) uses **interferon-gamma** obtained by recombinant DNA technology. It further comprises, as a stabilizer for the **interferon-gamma**, one or more of saccharides, salts, amino acids, serum albumins, gelatin, nonionic surfactants, glucuronic acid, dextrans and hydroxyethyl starches. (I) contains, in dose unit form, 0.1-106 units of **interferon-gamma**, in the form of a granule, sugarcoated agent, **troche** or enteric-coated agent. (I) contains 10-105 units of **interferon-gamma**/gram of agent.

TECHNOLOGY FOCUS - BIOLOGY - Preparation: The **interferon-gamma** may be of natural origin.

L119 ANSWER 11 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1999-611699 [53] WPIX
DNC C1999-178272
TI Compound alpha **interferon lozenge** and its preparing method - suitable for the treatment of hepatitis B, hepatitis C and other viral infections and tumor.
DC B04
IN CAO, X; JU, D; TAO, Q

PA (HUAC-N) HUACHEN BIOLOGICAL TECHNOLOGY INST SHANG
CYC 1
PI CN 1227125 A 19990901 (199953)* 1p A61K038-21 <--
ADT CN 1227125 A CN 1998-105384 19980225
PRAI CN 1998-105384 19980225
IC ICM **A61K038-21**
ICS A61K009-20
AB CN 1227125 A UPAB: 19991215
Compound alpha **interferon lozenge** contains **low -dosage** natural human alpha **interferon** and interleukin 2 as effective components as well as medically acceptable supplementary materials. The present invention also provides the **lozenge** preparing process at low and normal temperature conditions. The **lozenge** is suitable for the treatment of hepatitis B, hepatitis C and other viral infection and tumor, and has the advantages of **low dosage**, high curative effect, high tolerance of patient, stable performance, etc.
Dwg.0
FS CPI
FA AB
MC CPI: B04-H02B; B04-H05A; B12-M11B; B14-A02; B14-H01B; B14-N12

L119 ANSWER 12 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1999-611698 [53] WPIX
DNC C1999-178271
TI Beta **interferon lozenge** and its preparing method - suitable for the treatment of viral infections and tumor.
DC B04
IN CAO, X; JU, D; TAO, Q
PA (HUAC-N) HUACHEN BIOLOGICAL TECHNOLOGY INST SHANG
CYC 1
PI CN 1227124 A 19990901 (199953)* 1p A61K038-21 <--
ADT CN 1227124 A CN 1998-105383 19980225
PRAI CN 1998-105383 19980225
IC ICM **A61K038-21**
ICS A61K009-20
AB CN 1227124 A UPAB: 19991215
Beta **interferon lozenge** contains **low-dosage** beta **interferon** as effective component and medically acceptable supplementary material. The present invention also provides the **lozenge** preparing process at low and normal temperature conditions. The **lozenge** is suitable for the treatment of viral infection and tumor, and has the advantages of obvious curative effect, low toxicity, stable performance, etc.
Dwg.0
FS CPI
FA AB
MC CPI: B04-H05B; B12-M11D; B14-A02; **B14-H01**

L119 ANSWER 13 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1999-394786 [33] WPIX
DNC C1999-115975
TI Products to treat transplant rejection, autoimmune, graft-versus-host disease, retroviral or lymphoproliferative disease.
DC B04 B05 D16 K08
IN DELLA BITTA, R; FRANKS, C R; BITTA, R D
PA (BIOI-N) BIOINNOVATION LTD
CYC 83
PI WO 9926660 A2 19990603 (199933)* EN 32p A61K047-48
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK

MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9912499 A 19990615 (199944)
ZA 9810759 A 20000726 (200042) 32p A61K000-00
EP 1032427 A2 20000906 (200044) EN A61K047-48
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001523731 W 20011127 (200204) 56p A61K047-48

ADT WO 9926660 A2 WO 1998-GB3509 19981125; AU 9912499 A AU 1999-12499 19981125; ZA 9810759 A ZA 1998-10759 19981125; EP 1032427 A2 EP 1998-955771 19981125, WO 1998-GB3509 19981125; JP 2001523731 W WO 1998-GB3509 19981125, JP 2000-521861 19981125

FDT AU 9912499 A Based on WO 9926660; EP 1032427 A2 Based on WO 9926660; JP 2001523731 W Based on WO 9926660

PRAI GB 1997-24838 19971126

IC ICM A61K000-00; A61K047-48
ICS A61K038-00; A61K038-22; A61K045-00; A61P043-00

AB WO 9926660 A UPAB: 19990819

NOVELTY - A proliferatively active group linked to biologically active agent that preferentially or selectively affects proliferative cells, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for products comprising biologically active agent linked to a peptide hormone with a high affinity receptor or their functional equivalents.

ACTIVITY - Anti-proliferative; immunosuppressant; anti-retroviral; anticancer; immunostimulatory.

MECHANISM OF ACTION - Nucleotide synthesis modulation; gene sequence modulation; antisense nucleotide sequence modulation; reverse-transcriptase inhibitor.

DNA and RNA modulation results in cell death when the intracellular concentration of e.g. interleukin (IL)-2 overcomes the natural mechanisms of DNA repair and cell recovery.

USE - The product is useful as pharmaceuticals and in the manufacture of medicaments for treatment or prevention of diseases or disorders involving cells bearing a high affinity receptor for a proliferatively active group including autoimmune diseases, transplant rejection, graft-versus-host disease (GVHD), retroviral disease or lymphoproliferative disease (claimed). The product is also useful for:

(i) manufacturing medicaments for internalizing biologically active agent into cells (claimed),

(ii) delivering pharmacologically desirable species to cells whose proliferation is not desired,

(iii) treating diseases in which lymphocyte is mainly involved in tissue damage, autoimmune disorders in which immune attack on target organs is due to abnormal recognition of tissue antigens and/or cellular antigens by the immune system, particularly T lymphocytes, including autoimmune diabetes mellitus, autoimmune thyroiditis, autoimmune hepatitis, rheumatoid arthritis, autoimmune nephritis, uveitis, (Behcet's syndrome), multiple sclerosis, Sjogren syndrome, scleroderma, dermatopolimyositis, systemic lupus erythematosus, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, autoimmune neutropenia, vasculitis, Crohn's disease, ulcerative colitis, coeliac disease, psoriasis, sarcoidosis, atopic syndromes, HIV infection, lymphoproliferative diseases including lymphoblastic leukemia and lymphomas (erythroleukemia, chronic myeloid leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, acute monocytic leukemia, monomyelocytic leukemia, Wegener's disease, granulomatosis, inflammatory breast cancer, giant cellular vasculitis, histiocytic necrotizing lymphoadenitis (Kikuchi's disease), eosinophilic syndromes (Wegener, polymyositis, granulomatosis, systemic allergic skin reactions, parasitosis), myelodysplastic syndrome, breast cancer, malignant transformation of the bone (osteosarcoma, chondrosarcoma, fibrosarcoma) and fibrodysplastic syndromes (scleroderma), anti-angiogenesis (adenocarcinomas), thalassemia, sickle-cell anemia, breast adenocarcinoma,

congenital immunodeficiencies (Di George's syndrome, Nezelof's syndrome, ataxia-teleangiectasia, X-linked gammaglobulinemia), selective deficiency of T-lymphocyte function (inherited purine nucleoside phosphorylase deficiency) and congenital macrophage enzymatic monogenic deficiencies in lysosomal storage diseases (lipid storage disorders, mucopolysaccharidoses and glycoprotein storage diseases characterized by mono-enzymatic defects such as Gaucher's disease, fucosidosis, Farber's disease and Tay-Sachs syndrome.

ADVANTAGE - The product uses proliferatively active compounds as active vectors for pharmacologically active compounds such as drugs or genes, and allows drugs or genetic materials to be targeted into specific cell lineages that are predominantly responsible for clinical events. The product is a combination of two existing groups, both of which retain their function.

The product can be administered at exceedingly **low dosages**, producing little or no systemic toxicity and can stimulate the immune system, inducing a therapeutic effect.

The product has predictable and good biodistribution, shows good targeting and has low immunogenicity. Highly specific immunosuppression can be achieved maximizing the efficacy of immunosuppressive drugs and abrogating most toxicities.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B02-C01; B04-H02B; B04-H04B; B04-H05; B04-H06; B04-H06G; B04-H08; B14-A02A; B14-G01; B14-G02; **B14-H01**; D05-H12E; K08-X

TECH UPTX: 19990819

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred product: The link between the agent and the group is intracellularly cleavable, preferably by acid hydrolysis.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Proliferatively Active Group: The proliferatively active group is a cytokine (preferably interleukin (IL-2 or -6), tumor necrosis factor (TNF-alpha), macrophage colony-stimulating factor (M-CSF), **interferon** (**IFN**-alpha, beta or **gamma**), fibroblast growth factor, insulin-like growth factor (IGF), transforming growth factor (TGF-beta), granulocyte-macrophage colony-stimulating factor, stem-cell factor (SCF), granulocyte-colony-stimulating factor or erythropoeitin (epo)) or growth factor (epo, GM-CSF, G-CSF, SCF, multi-CSF (IL-3), M-CSF, E-CSF (IL-5), IGF, platelet-derived growth factor (PDGF) or TFG-beta2) or functionally equivalent molecule. The proliferatively active group is preferably a human cytokine or growth factor, preferably recombinant human cytokine or growth factor optionally modified by one or more amino acid modifications, more preferably recombinant IL-2 especially desala1-IL-2 ser125, and the molecule is functionally equivalent.

Preferred biologically active agent: The biologically active agent is an anti-proliferative drug that interferes with nucleotide synthesis, a gene sequence or antisense nucleotide sequence, preferably cyclosporin, FKK 506, thalidomide, dihydrofolate inhibitor, antiblastic drug, platinum coordination complex, vinca alkaloid, purine analog, pyrimidine analog, corticosteroid, viral reverse-transcriptase inhibitor or antisense nucleotide sequence, an immunosuppressant, enzyme inhibitor, anti-cancer drug or radioisotope, or methotrexate, azathioprine, cyclophosphamide, actinomycin D, daunorubicin, doxorubicin, bleomycin, rhenium radioisotope, yttrium radioisotope, 3'-azido-3'-deoxythymidine, antisense nucleotide sequence that binds to a viral nucleotide sequence or an anti-oncogene nucleotide sequence.

Preferred target: The target cells of the proliferatively active group have high affinity receptors for the group.

L119 ANSWER 14 OF 31 WPIX (C) 2002 THOMSON DERWENT

AN 1998-603242 [51] WPIX

DNC C1998-180685

TI Agent for treatment of infectious molluscum - contains **interferon** .
DC B04
PA (MOCH) MOCHIDA PHARM CO LTD
CYC 1
PI JP 10273449 A 19981013 (199851)* 4p A61K038-21 <--
ADT JP 10273449 A JP 1997-77260 19970328
PRAI JP 1997-77260 19970328
IC ICM **A61K038-21**
ICS A61K009-20
AB JP 10273449 A UPAB: 19981223
Treatment agent for buccal administration for treatment of infectious molluscum contains **interferon**.
The **interferon** is preferably **interferon** alpha .
The dosage form of the agent includes tablets (**troches**), chewable tablets, gels, pastes and gargles. The content of **interferon** per tablet is 0.1-10000 (especially 10-1000) IU. The dosage is at most 50000 (especially 10-1000) IU. The **interferon** in the agent is absorbed through the mucous membrane of the oral cavity.
USE - The agent is useful for treatment of infectious molluscum.
ADVANTAGE - The agent uses a **low dose** of **interferon** without side effects.
Dwg.0/1
FS CPI
FA AB
MC CPI: B04-H05A; B14-A02; B14-N17

L119 ANSWER 15 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1998-603241 [51] WPIX
DNC C1998-180684
TI **Oral remedy** for atopic disease - comprises **interferon** as active ingredient.
DC B04
PA (MOCH) MOCHIDA PHARM CO LTD
CYC 1
PI JP 10273448 A 19981013 (199851)* 4p A61K038-21 <--
ADT JP 10273448 A JP 1997-77259 19970328
PRAI JP 1997-77259 19970328
IC ICM **A61K038-21**
ICS A61K009-20
AB JP 10273448 A UPAB: 19990122
An **oral remedy** for atopic disease (especially atopic dermatitis) for oral application (preferably in tablet form) contains (especially 1-5000 IU) **interferon** (especially **interferon** alpha) as the active ingredient.
USE - The remedy is useful for curing atopic disease by oral application.
ADVANTAGE - Oral application of the remedy is safe and effective for curing atopic disease with a **low dose** without serious side effects, which has been seen in steroidal treatments, and therefore is useful in medicine.
Dwg.1/1
FS CPI
FA AB; GI
MC CPI: B04-H05A; B04-H05B; **B04-H05C**; B14-N17

L119 ANSWER 16 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1998-532485 [46] WPIX
DNC C1998-159838
TI Homeopathic immunostimulant for treatment of e.g. cancer - comprises lanthanide oxide compounds and optionally semi-conductor elements.
DC B06 P42
PA (JAKO-I) JAKOBY M

CYC 1
PI AT 9701686 A 19980915 (199846)* 11p A61K033-24
AT 405017 B 19990315 (199916) A61K033-24
ADT AT 9701686 A AT 1997-1686 19971006; AT 405017 B AT 1997-1686 19971006
FDT AT 405017 B Previous Publ. AT 9701686
PRAI AT 1997-1686 19971006
IC ICM A61K033-24
ICS A61K033-00
AB AT 9701686 A UPAB: 19981118
An immunostimulant agent comprises homeopathic dosages of neodymium oxide D8 or D9, gadolinium oxide D8 or D9, erbium oxide D8 or D9 and ytterbium oxide D8 or D9 and is present as a first formulation (A). The agent also preferably comprises homeopathic dosages of gallium arsenide and indium antimonide present as a second formulation (B). Formulation (B) can also conveniently contain zinc orotate, especially D4, terbium oxide, especially D5, metallic germanium, especially D4, germanite, especially D4, and molybdanite, especially D4.
USE - The agent is useful for the treatment of chronic illnesses and cancer. Components of formulation (A) (lanthanide elements) provide **low doses** of coherent radiation which inhibit antibodies and growth of cancer cells. Moreover, these components enhance the beneficial effects of selenium not only in retarding division of cancer cells, but also as a radical scavenger. Components of formulation (B) (semi-conductor elements) activate the lymphokines interleukin-1, interleukin-2 and **gamma -interferon**. Formulations (A) and (B) can be administered simultaneously ab initio. Alternatively, (A) can be administered initially and (B) can be introduced later, e.g. 1-2 weeks later. (A) is administered in a dosage of 20 drops 3 times daily. Administration of (B), which can be made up as a powder, tablet or globules, is in the form of a trituration with lactose in a dosage of one level coffee spoon 3 times daily.
Dwg.0/0
FS CPI GMPI
FA AB
MC CPI: B05-A03; B14-G01; **B14-H01**; B14-H01B

L119 ANSWER 17 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1998-054914 [06] WPIX
DNC C1998-019030
TI Genomic DNA encoding polypeptide inducing **interferon-gamma** production - by immuno-competent cells, useful to treat e.g. human malignant tumours or viral diseases.
DC B04 D16
IN KURIMOTO, M; OKURA, T; TORIGOE, K
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU
CYC 20
PI EP 816499 A2 19980107 (199806)* EN 74p C12N015-19
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 10080288 A 19980331 (199823) 39p C12N015-09
US 6060283 A 20000509 (200030) C12N015-24
ADT EP 816499 A2 EP 1997-304616 19970627; JP 10080288 A JP 1997-187418 19970627; US 6060283 A US 1997-884324 19970627
PRAI JP 1996-185305 19960627
IC ICM C12N015-09; C12N015-19; C12N015-24
ICS C07H021-04; C07K001-22; C07K001-36; C07K014-52; C12N001-21; C12N005-10; C12P021-02
ICA A61K038-00; **A61K038-21**; A61K048-00
ICI C12N001-21, C12R001:19; C12N005-10, C12R001:91; C12P021-02, C12R001:91; C12P021-02, C12R001:19
AB EP 816499 A UPAB: 19980209
Genomic DNA encoding polypeptide with 157 amino acid sequence (I) (or homologous sequence) which induces **interferon-gamma** (**IFN- gamma**) production by immunocompetent cells is new.

USE - The polypeptide has high biological activity, including enhancing cytotoxicity of killer cells and inducing killer cell formation in addition to inducing **IFN- gamma** production by immunocompetent cells when expressed in mammalian cells, facilitating its use in **low dosages** to treat/prevent e.g. malignant tumours, viral, bacterial infectious and immune diseases. Because it is expressed in mammalian cells, the polypeptide also has low toxicity when used in human treatments, minimising side effects. The DNA is also useful in gene therapy (e.g. by injecting vectors containing DNA or transplanting cells) for such diseases.

ADVANTAGE - The DNA is expressible in mammalian cells, making the polypeptide especially suitable for human therapeutic use, since intracellular enzyme processing is similar to that in human cells (excluded due to low production). The polypeptide yield/culture by mammalian cell transformants was higher than prior art expression of sequence (IV) in Escherichia coli (15 versus 5 mg/l) and the polypeptide had higher biological activity, e.g. induced 3.4 x 105 versus 1.7 x 105 IU **IFN- gamma** production in immunocompetent human lymphocytes.

Dwg.0/1

FS CPI
FA AB
MC CPI: B04-E02F; B04-E08; B04-F0200E; B04-G0100E; B04-H05C0E; B04-N02; D05-H12A; D05-H12E; D05-H14; D05-H17A6

L119 ANSWER 18 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1998-041699 [04] WPIX
DNN N1998-033460 DNC C1998-013851
TI Product providing gradual release of **low doses** of cytokine, especially interleukin-2 - for chronic treatment or prevention of infection, immune deficiency, cancer etc. without side effects associated with short term, high dose regimens.
DC A96 B04 B07 P32 P34
IN SMITH, K A
PA (CORR) CORNELL RES FOUND INC
CYC 73
PI WO 9741831 A1 19971113 (199804)* EN 54p A61K009-06
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU
AU 9730613 A 19971126 (199813) A61K009-06
EP 901370 A1 19990317 (199915) EN A61K009-06
R: DE FR GB IT NL SE
JP 2000510122 W 20000808 (200043) 54p A61K038-00
ADT WO 9741831 A1 WO 1997-US7787 19970507; AU 9730613 A AU 1997-30613 19970507; EP 901370 A1 EP 1997-925488 19970507, WO 1997-US7787 19970507; JP 2000510122 W JP 1997-540196 19970507, WO 1997-US7787 19970507
FDT AU 9730613 A Based on WO 9741831; EP 901370 A1 Based on WO 9741831; JP 2000510122 W Based on WO 9741831
PRAI US 1996-646098 19960507
REP 1.Jnl.Ref; US 4933433; US 4938956; US 4940456; US 5126129; US 5420109
IC ICM A61K009-06; A61K038-00
ICS A61F013-00; A61K009-00; A61K009-08; A61K009-10; A61K009-107; A61K009-12; A61K009-127; A61K009-14; A61K009-20; A61K009-28; A61K009-40; A61K009-48; A61K009-50; A61K009-52; A61K009-70; A61K038-18; A61K038-19; A61K038-20; **A61K038-21**; A61K038-22; A61K039-00; A61K045-00; A61M015-00; A61M015-08; A61P029-00; A61P031-02; A61P031-04; A61P031-12; A61P031-18; A61P035-00
AB WO 9741831 A UPAB: 19980126
Product (A) contains at least 1 agent (I) with cytokine activity and releases a desired amount of (I) over a predetermined period.

(I) is any of interleukin (IL)-2 to -15; tumour necrosis factor alpha or beta ; nerve growth factor; the CD40, Fas, CD27 or CD30 ligands; **interferons** (**IFN**) alpha , beta or **gamma** ; macrophage inhibiting protein or Rantes, or their active fragments, analogues or derivatives.

Also claimed are:
(1) topical kits,
(2) inhalation devices,
(3) self-administration kits,
(4) transdermal delivery devices and
(5) implants containing (A).

USE - (A) provide chronic stimulation, inhibition and/or maintenance of an immune response, particularly for treating or preventing, in humans or animals, microbial infections (including those that may occur after bone marrow transplant); congenital or acquired immune deficiency; inflammation; sepsis; necrosis or malignant disease, particularly in subjects seropositive for human immunodeficiency virus (HIV) or with carcinoma, melanoma, sarcoma, leukaemia, lymphoma or myeloma.

Specifically treatment with (I) increases the count of lymphocytes, monocytes and/or polymorphonuclear leucocytes. (A) is also useful as an adjuvant for vaccines.

(A) releases (I) at 1-100 nmole/m2 of body area/day. (A) are administered by injection, orally, intranasally, by inhalation or from implants.

ADVANTAGE - Chronic administration of **low doses** of (I) activates the immune system without significant toxic side effects, even when continued for several years. (A) can be self-administered and provide general and/or specific modulation of an immune response, including in children and elderly people. At **low doses** there is no need to interrupt treatment or administer blocking agents to limit side effects. When applied to subjects with HIV, the **low dose** of (I) does not stimulate proliferation of virus or opportunistic pathogens.

Dwg.0/0

FS CPI GMPI
FA AB
MC CPI: A12-V01; B04-H02B; B04-H05; B04-H06D; B04-H08; B14-G01

L119 ANSWER 19 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1998-008441 [01] WPIX
CR 1997-558691 [51]; 1998-008440 [01]
DNC C1998-002919
TI Treating neoplasia by oro-mucosal administration of **low doses** of **interferon** - especially where tumours are of non-viral origin, avoids systemic side effects.
DC B04
IN KAIDO, T J; TOVEY, M G
PA (PHAR-N) PHARMA PACIFIC PTY LTD
CYC 77
PI WO 9741886 A1 19971113 (199801)* EN 40p A61K038-21 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9727109 A 19971126 (199813) A61K038-21 <--
EP 898478 A1 19990303 (199913) EN A61K038-21 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
CN 1218407 A 19990602 (199940) A61K038-21 <--
JP 2000504027 W 20000404 (200027) 35p A61K038-21 <--
NZ 332688 A 20000728 (200043) A61K038-21 <--
AU 724190 B 20000914 (200051) A61K038-21 <--
ZA 9703995 A 20001025 (200061) 34p A61K000-00

BR 9709223 A 20001212 (200102) A61K038-21 <--
KR 2000010880 A 20000225 (200102) A61K038-21 <--

ADT WO 9741886 A1 WO 1997-IB594 19970505; AU 9727109 A AU 1997-27109 19970505; EP 898478 A1 EP 1997-920907 19970505, WO 1997-IB594 19970505; CN 1218407 A CN 1997-194500 19970505; JP 2000504027 W JP 1997-539703 19970505, WO 1997-IB594 19970505; NZ 332688 A NZ 1997-332688 19970505, WO 1997-IB594 19970505; AU 724190 B AU 1997-27109 19970505; ZA 9703995 A ZA 1997-3995 19970508; BR 9709223 A BR 1997-9223 19970505, WO 1997-IB594 19970505; KR 2000010880 A WO 1997-IB594 19970505, KR 1998-709024 19981109

FDT AU 9727109 A Based on WO 9741886; EP 898478 A1 Based on WO 9741886; JP 2000504027 W Based on WO 9741886; NZ 332688 A Based on WO 9741886; AU 724190 B Previous Publ. AU 9727109, Based on WO 9741886; BR 9709223 A Based on WO 9741886; KR 2000010880 A Based on WO 9741886

PRAI AU 1996-9765 19960509

REP 4.Jnl.Ref; AU 8812227; US 4605555; US 5286748

IC ICM A61K000-00; **A61K038-21**
ICS A61K038-00; A61K045-00; A61K051-00; A61P035-00; A61P035-02

AB WO 9741886 A UPAB: 20010207
Treatment of neoplasia in mammals comprises administration, by oro-mucosal contact, of 1500-20 million international units (IU) of **interferon** (IFN), provided the dose is lower than a dose that would cause a pathological response if given parenterally.

USE - The method is specifically used to treat neoplasms of non-viral aetiology, e.g. multiple myeloma, leukaemias, lymphomas, carcinomas, glioblastoma, lung cancer, malignant melanoma or brain tumours, including formation of metastases.

ADVANTAGE - Oro-mucosal administration is (almost) as effective at parenteral delivery, but active IFN does not enter the blood and IFN-inducible marker genes are not stimulated.

IFN administered oro-mucosally probably stimulates the lymphoid tissue around the oropharyngeal cavity.

Dwg.0/0

FS CPI
FA AB
MC CPI: B04-H05; **B14-H01**

L119 ANSWER 20 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1998-008440 [01] WPIX
CR 1997-558691 [51]; 1998-008441 [01]
DNC C1998-002918
TI Stimulating host defence by oro-mucosal administration of **low doses** of **interferon** - for treatment of auto-immune, mycobacterial, neuro-degenerative, parasitic and viral diseases, without causing systemic side effects.
DC B04
IN TOVEY, M G
PA (PHAR-N) PHARMA PACIFIC PTY LTD
CYC 77
PI WO 9741883 A1 19971113 (199801)* EN 39p A61K038-21 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9723992 A 19971126 (199813) A61K038-21 <--
ZA 9703988 A 19990127 (199910) 43p A61K000-00
CN 1218409 A 19990602 (199940) A61K038-21 <--
EP 956040 A1 19991117 (199953) EN A61K038-21 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
BR 9709066 A 20000104 (200019) A61K038-21 <--
JP 2000504026 W 20000404 (200027) 38p A61K038-21 <--
NZ 332690 A 20000728 (200043) A61K038-21 <--
KR 2000010882 A 20000225 (200102) A61K038-41

AU 729514 B 20010201 (200112) A61K038-21 <--
ADT WO 9741883 A1 WO 1997-IB489 19970505; AU 9723992 A AU 1997-23992 19970505; ZA 9703988 A ZA 1997-3988 19970508; CN 1218409 A CN 1997-194504 19970505; EP 956040 A1 EP 1997-919563 19970505, WO 1997-IB489 19970505; BR 9709066 A BR 1997-9066 19970505, WO 1997-IB489 19970505; JP 2000504026 W JP 1997-539695 19970505, WO 1997-IB489 19970505; NZ 332690 A NZ 1997-332690 19970505, WO 1997-IB489 19970505; KR 2000010882 A WO 1997-IB489 19970505, KR 1998-709026 19981109; AU 729514 B AU 1997-23992 19970505
FDT AU 9723992 A Based on WO 9741883; EP 956040 A1 Based on WO 9741883; BR 9709066 A Based on WO 9741883; JP 2000504026 W Based on WO 9741883; NZ 332690 A Based on WO 9741883; KR 2000010882 A Based on WO 9741883; AU 729514 B Previous Publ. AU 9723992, Based on WO 9741883
PRAI AU 1996-9765 19960509
REP 4.Jnl.Ref; US 4605555; US 5286748
IC ICM A61K000-00; **A61K038-21**; A61K038-41
ICS A61K038-00; A61K045-08; A61P003-10; A61P015-00; A61P019-02; A61P025-00; A61P031-00; A61P031-06; A61P031-12; A61P031-14; A61P031-18; A61P031-22; A61P033-00; A61P033-06; A61P035-00; A61P037-00
AB WO 9741883 A UPAB: 20010207
Host defence mechanisms in a mammal are stimulated by administering an **interferon** (IFN) by oro-mucosal contact at doses of 5000-20 million international units (IU), provided that the dose used would not induce a pathological response if given parenterally.Also new is administration of IFN at 1500-20 million IU, by the same route, for treatment of autoimmune, mycobacterial, neurodegenerative, parasitic or viral diseases.

USE - Specifically the treatment is used in cases of arthritis, diabetes, lupus, multiple sclerosis, leprosy, tuberculosis, encephalitis, Creutzfeldt-Jakob disease, malaria (particularly to prevent progression to the cerebral form), cervical cancer, genital herpes, hepatitis B or C, human immunodeficiency virus, human papilloma virus or herpes simplex virus 1 or 2, but other virus infections which may be treated are disclosed.

ADVANTAGE - When given oro-mucosally, **low doses** of IFN are (almost) as effective as the same doses given parenterally, but when administered this way active IFN does not enter the blood and does not induce IFN-inducible marker genes. IFN administered oro-mucosally probably stimulates the lymphoid tissue around the nasopharyngeal and oral cavities.

Dwg.0/0
FS CPI
FA AB
MC CPI: B04-H05; **B14-A01B1**; B14-A02; B14-A02B1; B14-B02; B14-B04B3; B14-C09; B14-G02D; **B14-H01**; B14-J01; B14-J01A4; B14-N12; B14-S04

L119 ANSWER 21 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1997-457199 [42] WPIX
DNC C1997-145898
TI Use of natural human alpha-**interferon** - in preparation of liquid medicaments for peroral administration for treating viral infections, neoplasia and immune diseases.
DC B04 D16
IN BROZZO, R; TARRO, G
PA (UNIH-N) UNIHART CORP; (IFIF-N) IFI IST FARMACOTERAPICO ITAL SPA; (FARM-N) IST FARMACOTERAPICO ITAL SPA; (FARM-N) IST FARMACOTERAPEUTICO ITAL SPA
CYC 77
PI WO 9731649 A1 19970904 (199742)* EN 18p A61K038-21 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW

MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU
AU 9722299 A 19970916 (199803) A61K038-21 <--
EP 886527 A1 19981230 (199905) EN A61K038-21 <--
R: AT BE CH DE DK ES FR GB GR IE LI LT LU LV NL PT SE
IT 1283945 B 19980507 (200002) A61K000-00
IT 1284852 B 19980522 (200011) A61K000-00
HU 9902188 A2 20000128 (200015) A61K038-21 <--
BR 9707772 A 20000104 (200019) A61K038-21 <--
JP 2000506839 W 20000606 (200035) 18p A61K038-21 <--
AU 722987 B 20000817 (200044) A61K038-21 <--
KR 99082559 A 19991125 (200055) A61K038-21 <--
EP 886527 B1 20010912 (200155) EN A61K038-21 <--
R: AT BE CH DE DK ES FR GB GR IE LI LT LU LV NL PT SE
DE 69706657 E 20011018 (200169) A61K038-21 <--
ES 2160927 T3 20011116 (200201) A61K038-21 <--

ADT WO 9731649 A1 WO 1997-IT40 19970227; AU 9722299 A AU 1997-22299 19970227; EP 886527 A1 EP 1997-905395 19970227, WO 1997-IT40 19970227; IT 1283945 B IT 1996-RM136 19960228; IT 1284852 B IT 1996-RM427 19960614; HU 9902188 A2 WO 1997-IT40 19970227, HU 1999-2188 19970227; BR 9707772 A BR 1997-7772 19970227, WO 1997-IT40 19970227; JP 2000506839 W JP 1997-530771 19970227, WO 1997-IT40 19970227; AU 722987 B AU 1997-22299 19970227; KR 99082559 A WO 1997-IT40 19970227, KR 1998-706297 19980814; EP 886527 B1 EP 1997-905395 19970227, WO 1997-IT40 19970227; DE 69706657 E DE 1997-606657 19970227, EP 1997-905395 19970227, WO 1997-IT40 19970227; ES 2160927 T3 EP 1997-905395 19970227

FDT AU 9722299 A Based on WO 9731649; EP 886527 A1 Based on WO 9731649; HU 9902188 A2 Based on WO 9731649; BR 9707772 A Based on WO 9731649; JP 2000506839 W Based on WO 9731649; AU 722987 B Previous Publ. AU 9722299, Based on WO 9731649; KR 99082559 A Based on WO 9731649; EP 886527 B1 Based on WO 9731649; DE 69706657 E Based on EP 886527, Based on WO 9731649; ES 2160927 T3 Based on EP 886527

PRAI IT 1996-RM427 19960614; IT 1996-RM136 19960228

REP 3.Jnl.Ref; WO 8803411

IC ICM A61K000-00; **A61K038-21**
ICS A61K009-08

AB WO 9731649 A UPAB: 19990107
The following are claimed: (A) use of natural human alpha - **interferon** for preparation of medicaments in liquid form, to be administered by the peroral route at dosages of 100-500 IU/day, for (i) therapy of viral hepatitis, or (ii) therapy of neoplasia and immunological diseases, in humans and animals; and (B) a pharmaceutical liquid composition for peroral administration, comprising natural human alpha - **interferon** (either from lymphoblastoid cell cultures or from lymphocyte cells) at a concentration of 100-500 IU/ml.

The **interferon** is obtained from lymphoblastoid cell cultures or from lymphocyte cells. The medicament is administered in monodosage units of approximately 1 ml.

USE - The medicaments may be used in treatment of viral infections (especially viral hepatitis), neoplasia and immunological diseases (especially immunodeficiency syndromes).

ADVANTAGE - The **low dosages** contained in the medicaments reduce the risk of side effects. The medicaments are in a form which is generally acceptable to patients.

Dwg.0/0

FS CPI

FA AB

MC CPI: B04-H05; B14-A02A; B14-G01; B14-G02D; B14-N12; D05-H09

L119 ANSWER 22 OF 31 WPIX (C) 2002 THOMSON DERWENT

AN 1994-103034 [13] WPIX

DNC C1994-047473

TI New sugar-modified cytokine - comprising a glycosyl modifying gp. bound to primary amino gp. of cytokine.

DC B04
IN DOKEN, K; HAMAGUCHI, N; SATO, J; SATO
PA (TAKE) TAKEDA CHEM IND LTD; (TAKE) TAKEDA PHARM IND CO LTD
CYC 21
PI EP 589378 A2 19940330 (199413)* EN 29p C07K015-14
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
CA 2106821 A 19940325 (199423) C07K015-26
JP 06345795 A 19941220 (199510) 18p C07K003-08
CN 1087916 A 19940615 (199531) C07K015-26
EP 589378 A3 19950222 (199541) C07K015-14
TW 263437 A 19951121 (199607) A61K037-66
US 5643564 A 19970701 (199732) 22p A61K038-70
ADT EP 589378 A2 EP 1993-115060 19930918; CA 2106821 A CA 1993-2106821 19930923; JP 06345795 A JP 1993-236482 19930922; CN 1087916 A CN 1993-117879 19930923; EP 589378 A3 EP 1993-115060 19930918; TW 263437 A TW 1993-107513 19930914; US 5643564 A Cont of US 1993-124868 19930922, US 1995-455661 19950531
PRAI JP 1992-254962 19920924; JP 1993-88920 19930415
REP No-SR.Pub; EP 251304; US 5096816
IC ICM A61K037-66; A61K038-70; C07K003-08; C07K015-14; C07K015-26
ICS A61K037-02; **A61K038-21**; A61K047-42; A61K047-48; C07K014-54; C07K014-555
AB EP 589378 A UPAB: 19940517
Sugar-modified cytokine (A) comprises binding a modifying gp. of formula R-X- (I) to at least one primary amino gp. of a cytokine. R = glycosyl; t = 3-6; X = C6H4-NH-CS-, S-CH2-CO-NH-CH2-CH2, OCH2CH2, CS-NH-C6H3(CH3)-NHCS, CO(CH2)t-CO, CO-CH(OH)-CH(OH)-CO, CONH, etc.
The cytokine is pref. an **interferon**-L and the primary amino gp. is the E-amino gp. of a lysine residue or the X-amino gp. of the N-terminal amino acid residue. The glycosyl is a glycopyranosyl selected from galactopyranosyl, mannopyranosyl, glucopyranosyl or furopyranosyl.
USE/ADVANTAGE - The sugar-modified cytokine ensures migration of almost all the dose of cytokine to the liver rapidly after admin. to the live body. (A) is used in antitumoural or antiviral therapy, esp. liver disease therapy. For antitumoural therapy, (A) is injected at a dose of (0.01-1.0) x 400,000 units/day and for treatment of e.g. hepatitis B or C at a dose of (0.1-100) x 10power-5 units/day. (A) provides quicker elimination from the serum and quicker migration to the liver compared to corresponding known non-modified cytokine. (A) offers a therapeutic effect at **low doses** because it is efficiently transported to the target organ. (A) has few side effects such as fever and chilling and low toxicity.
Dwg.0/6
FS CPI
FA AB; GI; DCN
MC CPI: B04-D01; B04-H05A; B14-A02; **B14-H01**; B14-N12
ABEQ US 5643564 A UPAB: 19970806
A sugar-modified interleukin-2 which comprises two to five modifying groups, which may be the same or different, bound to at least one primary amine group of interleukin-2, wherein said modifying group is represented by the formula (I):
R-X-(I)
wherein R represents a glycosyl group;
X represents -OCH(CH(OH)-CH2OH)-CH(OH)CH(OH)CH2, C6H4-NH-CS, -S-CH2-CO-NH-CH2-CH2-, O-CH2-CH2-, -CS-NH-C6H3(CH3)-NHCS-, -CO-CH(OH)-CH(OH)-CO- or formula (a) wherein Y is selected from a group of (i), (ii) or (iii)
wherein Y is of the same meaning as mentioned above, -CO-NH- or -O-CH(CH(OH)CH2(OH))-CH(OH)-CH(OH)-CO-.

Dwg.0/0

L119 ANSWER 23 OF 31 WPIX (C) 2002 THOMSON DERWENT

AN 1993-288863 [37] WPIX
CR 1988-147503 [21]
DNC C1993-128916
TI Oral, immuno-therapeutic interferon compsn. for treating e.g. multiple sclerosis, rheumatoid arthritis etc. - comprises interferon e.g. alpha or beta interferon and excipient which promotes contact of interferon with oral and pharyngeal mucosa.
DC B04
IN **CUMMINS, J M**
PA (TEXA) UNIV TEXAS A & M SYSTEM
CYC 2

PI	CA 1320905	C	19930803 (199337)*	36p	A61K037-66
	US 5817307	A	19981006 (199847)		A61K038-21 <--
	US 5824300	A	19981020 (199849)		A61K038-21 <--
	US 5830456	A	19981103 (199851)		A61K038-21 <--
	US 5846526	A	19981208 (199905)		A61K038-21 <--
	US 5882640	A	19990316 (199918)		A61K038-21 <--
	US 6372218	B1	20020416 (200232)		A61K039-00

ADT CA 1320905 C CA 1987-550816 19871102; US 5817307 A CIP of US 1986-927834 19861106, Cont of US 1987-110501 19871026, Cont of US 1992-875071 19920428, Cont of US 1993-9353 19930126, Div ex US 1994-305418 19940913, US 1995-484376 19950607; US 5824300 A CIP of US 1986-927834 19861106, Cont of US 1987-110501 19871026, Cont of US 1992-875071 19920428, Cont of US 1993-9353 19930126, Div ex US 1994-305418 19940913, US 1995-479958 19950607; US 5830456 A CIP of US 1986-927834 19861106, Cont of US 1987-110501 19871026, Cont of US 1992-875071 19920428, Cont of US 1993-9853 19930126, US 1994-305418 19940913; US 5846526 A CIP of US 1986-927834 19861106, Cont of US 1987-110501 19871026, Cont of US 1992-875071 19920428, Cont of US 1993-9353 19930126, Div ex US 1994-305418 19940913, US 1995-476621 19950607; US 5882640 A CIP of US 1986-927834 19861106, Cont of US 1987-110501 19871026, Cont of US 1992-875071 19920428, Cont of US 1993-9353 19930126, Div ex US 1994-305418 19940913, US 1995-475753 19950607; US 6372218 B1 CIP of US 1986-927834 19861106, Div ex US 1987-110501 19871026, Cont of US 1991-775291 19911009, Cont of US 1993-3624 19930113, US 1995-381136 19950131
PRAI US 1987-110501 19871026; US 1986-927834 19861106; US 1992-875071 19920428; US 1993-9353 19930126; US 1994-305418 19940913; US 1995-484376 19950607; US 1995-479958 19950607; US 1993-9853 19930126; US 1995-476621 19950607; US 1995-475753 19950607; US 1991-775291 19911009; US 1993-3624 19930113; US 1995-381136 19950131
IC ICM A61K037-66; **A61K038-21**; A61K039-00
ICS A61K009-20; C07K014-00
AB CA 1320905 C UPAB: 20020521

An oval dosage form of interferon for nunan use comprises 0.01-5 IU of interferon per pound of body wt. and excipients selected to promote contact of interferon with the oral and pharyngeal mucosa of the patient.

Also claimed are (i) an immuno-therapeutic dosage formulation in the form of an effervescent tablet, which releases 0.01-5 IU of interferon per lb. of body wt. on effervescent dissolution in water and (ii) an immuno-therapeutic dosage form comprising 0.01-5 IU of interferon/lb. of body wt. and excipient allowing contact of interferon with the oral and pharyngeal mucosa of patient, which is held in the mouth.

USE/ADVANTAGE - Compsn. is used to potentiate disease-corrective immune responses in warm-blooded animals afflicted with immunoresistant diseases, characterised by hyper- or hypo-active immune system function. Compsns. are used to effect remission of neoplastic disease, hyperallergenicity, immuno-resistant or -debilitating viral infections and autoimmune disorders showing chronic tissue degenerative inflammation, e.g., multiple sclerosis, rheumatoid arthritis, stomatitis, lupus erythematosus, compsn. alone or in combination can be used to effect remission of cancers, e.g., malignant lymphoma, melanoma, mesotheliane, Burkitt lymphoma and nasopharyngeal carcinoma and other neoplastic

diseases. Human viral infections which compsns. can be used to treat are human rhinovirus (common cold), herpes simplex I virus (cold sores) and human papov (warts). Admin. is by dosages of 0.01-5 IU/lb. body wt./per day. Daily dosage is singularly or in a multiple-dose daily regimen. A staggered treatment of 1-3 days/week or month can be used as an alternative to continuous daily treatment.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: **B02-V03**; B12-A07; B12-C10; B12-D02; B12-D03; B12-E02; B12-G07; B12-M07; B12-M11B

L119 ANSWER 24 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1993-188452 [23] WPIX
DNC C1993-083431
TI Prevention of parasitic infection in animals or human exposed to parasite - by contact of oral and pharyngeal mucosa with alpha interferon, pref. to prevent East Coast Fever in cattle.
DC B04 C03
IN **CUMMINS, J M**; YOUNG, A S
PA (AMAR-N) AMARILLO CELL CULTURE CO
CYC 1
PI US 5215741 A 19930601 (199323)* 7p A61K037-66
ADT US 5215741 A US 1990-605687 19901030
PRAI US 1990-605687 19901030
IC ICM A61K037-66
AB US 5215741 A UPAB: 19931115
Treating a human or animal exposed to an infective parasitic agent comprises contacting the oral and pharyngeal mucosa with alpha interferon (I) in an amt. effective to prevent development of a parasite infection: (I) is pref. human leukocyte interferon.
USE - The method is esp. useful for preventing the development of East Coast Fever in cattle exposed to Theileria parva parva. Dosage is 0.1-10 IU (I)kg.
In an example, Eight Freisian bulls were weighed and randomly assigned to 1 of 2 treatment gps. The bulls were inoculated, by sic. injection. (day O) with a 10- dilution of a sporozoite stabilate of T.p. parva (marikebuni) stock (St IL 3014). Four of the cattle were treated daily with an oral liq. dosage contg. 1 IV/kg of human alpha-inferferon (Ia).
Dwg.0/1
FS CPI
FA AB
MC CPI: **B02-V03**; **C02-V03**; B12-B04; C12-B04

L119 ANSWER 25 OF 31 WPIX (C) 2002 THOMSON DERWENT
AN 1989-220466 [30] WPIX
DNC C1989-097969
TI Redn. of toxic side effects of cancer radiation therapy, etc. - by contact of oral and pharyngeal mucosa with interferon.
DC B04
IN **CUMMINS, J M**
PA (AMAR-N) AMARILLO CELL CULTURE CO
CYC 32
PI WO 8906139 A 19890713 (198930)* EN 27p
RW: AT BE CH DE FR GB IT LI LU NL OA SE
W: AU BB BG BR DK FI HU JP KP KR LK MC MG MW NO RO SD SU
AU 8929414 A 19890801 (198943)
DK 9001606 A 19900703 (199045)
EP 396616 A 19901114 (199046)
R: AT BE CH DE FR GB IT LI LU NL SE
US 5017371 A 19910521 (199123) 7p
JP 03504375 W 19910926 (199145)

HU 56720 T 19911028 (199147)
HU 206987 B 19930301 (199313) A61K037-66
EP 396616 B1 19940413 (199415) EN 8p A61K037-66
R: AT BE CH DE FR GB IT LI LU NL SE
DE 68914644 E 19940519 (199421) A61K037-66
EP 396616 A4 19911016 (199519)
CA 1336398 C 19950725 (199537) A61K037-66
JP 2813017 B2 19981022 (199847) 9p A61K038-21 <--

ADT WO 8906139 A WO 1989-US24 19890103; EP 396616 A EP 1989-901901 19890103; US 5017371 A US 1988-141621 19880106; JP 03504375 W JP 1989-501802 19890103; HU 206987 B HU 1989-950 19890103, WO 1989-US24 19890103; EP 396616 B1 EP 1989-901901 19890103, WO 1989-US24 19890103; DE 68914644 E DE 1989-614644 19890103, EP 1989-901901 19890103, WO 1989-US24 19890103; EP 396616 A4 EP 1989-901901 ; CA 1336398 C CA 1989-587392 19890103; JP 2813017 B2 JP 1989-501802 19890103, WO 1989-US24 19890103

FDT HU 206987 B Previous Publ. HU 56720, Based on WO 8906139; EP 396616 B1 Based on WO 8906139; DE 68914644 E Based on EP 396616, Based on WO 8906139; JP 2813017 B2 Previous Publ. JP 03504375, Based on WO 8906139

PRAI US 1988-141621 19880106

REP 2.Jnl.Ref; 02Jnl.Ref; WO 8200588; WO 8803411

IC ICM A61K037-66; **A61K038-21**
ICS A61K009-00; A61K045-00; A61K045-02

AB WO 8906139 A UPAB: 19930923
To reduce the side effects of cancer therapy by chemotherapeutic agents or radiation, the oral and pharyngeal mucosa of the patient receiving the therapy are contacted with interferon.

The interferon may be alpha- or beta-interferon, and is pref. human alpha-interferon. It may also be interferon of a non-human species or a semi-synthetic interferon. A patient receiving chemotherapy may be administered interferon daily during the chemotherapy, e.g. in an amt. of 0.1-5 IU/lb/day and beginning at least one day prior to the initiation of the chemotherapy. Pref. admin. is by a dosage form adapted to be held in the patient's mouth for a period of time to maximise contact with the oral and pharyngeal mucosa, such as a soln. or a lozenge.
0/0

FS CPI

FA AB

MC CPI: **B02-V03**; B12-G07

ABEQ US 5017371 A UPAB: 19930923
Process for reducing the side effects arising from the treatment of cancer patients with chemotherapeutic agents or radiation comprises admin. of alpha- and/or beta-interferone in the oral and pharyngeal mucosa zones. The interferone may be obtd. from human or non-human sources or by recombinant DNA technology and the dosage is about 0.1-5.0 international units of interferone per lb. body mass per day.

USE - The process improves and widens the application of chemotherapeutic agents and radiation for the treatment of cancer.

ABEQ EP 396616 B UPAB: 19940531
Use of interferon for the manufacture of a medicament in a buccal dosage form defined to release interferon in a patient's mouth for contact with the patient's oral and pharyngeal mucosa to reduce the toxic side effects resulting from the administration of cancer therapy, utilizing chemotherapeutic agents or radiation treatment, in the patient receiving such therapy for treatment of cancer, said buccal dosage form comprising interferon and a pharmaceutically acceptable carrier therefor, and providing 0.22 to 11 IU of interferon per kg (0.1 to 5 IU/lb) of patient body weight.
Dwg.0/0

L119 ANSWER 26 OF 31 WPIX (C) 2002 THOMSON DERWENT

AN 1988-147503 [21] WPIX

CR 1993-288863 [37]

DNC C1988-065713

TI Treatment of diseases with interferon - by contact with oral and pharyngeal mucosa.
DC B04 C03
IN **CUMMINS, J M**; CUMMINIS, J M
PA (TEXA) UNIV TEXAS A & M SYSTEM; (AMAR-N) AMARILLO CELL CULTURE CO
CYC 33
PI WO 8803411 A 19880519 (198821)* EN 46p
RW: AT BE CH DE FR GB IT LU NL OA SE
W: AU BB BG BR DK FI HU JP KP KR LK MC MG MW NO RO SD SU
ZA 8708295 A 19880503 (198830)
AU 8812227 A 19880601 (198841)
DK 8803743 A 19880905 (198848)
NO 8802983 A 19881024 (198848)
EP 341258 A 19891115 (198946) EN
R: AT BE CH DE FR GB IT LI LU NL SE
US 5019382 A 19910528 (199124) 9p
AU 9226345 A 19921203 (199304) A61K037-66
EP 341258 B1 19940302 (199409) EN 11p A61K037-66
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3789239 G 19940407 (199415) A61K037-66
EP 341258 A4 19901010 (199513)
NO 176995 B 19950327 (199517) A61K038-21 <--
SG 9500143 A 19951222 (199611)
KR 9603377 B1 19960309 (199911) A61K038-21 <--
DK 172974 B 19991025 (199951) A61K038-21 <--
ADT WO 8803411 A WO 1987-US2998 19871106; ZA 8708295 A ZA 1987-8295 19871105; EP 341258 A EP 1988-901169 19871106; US 5019382 A US 1990-465527 19900117; AU 9226345 A AU 1992-26345 19921009, Div ex AU 1988-12227 ; EP 341258 B1 WO 1987-US2998 19871106, EP 1988-901169 19871106; DE 3789239 G DE 1987-3789239 19871106, WO 1987-US2998 19871106, EP 1988-901169 19871106; EP 341258 A4 EP 1988-901169 19871106; NO 176995 B WO 1987-US2998 19871106, NO 1988-2983 19880705; SG 9500143 A SG 1995-143 19950126; KR 9603377 B1 WO 1987-US2998 19871106, KR 1988-700794 19880706; DK 172974 B WO 1987-US2998 19871106, DK 1988-3743 19880705
FDT EP 341258 B1 Based on WO 8803411; DE 3789239 G Based on EP 341258, Based on WO 8803411; NO 176995 B Previous Publ. NO 8802983; SG 9500143 A Previous Publ. EP 341258; DK 172974 B Previous Publ. DK 8803743
PRAI US 1986-927834 19861106
REP 2.Jnl.Ref; FR 2575655; US 4462985; US 4497795; 3.Jnl.Ref; EP 177342; JP 60116631; WO 8200588; 04Jnl.Ref
IC ICM A61K037-66; **A61K038-21**
ICS A61K009-20; A61K045-02; C07K000-00
AB WO 8803411 A UPAB: 19991207
Treatment of (a) autoimmune disorders characterised by chronic tissue-degenerative inflammation, esp. multiple sclerosis, rheumatoid arthritis, nasal solar dermatitis, stomatitis and lupus erythematosus, (b) neoplastic diseases, esp. malignant lymphoma, melanoma, mesothelioma, Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin's disease and leukaemia, (c) viral infections, esp. human rhinovirus, HSV I and II, viral myocarditis, AIDS, warts, feline leukaemia virus, feline infectious peritonitis, canine parvovirus and canine herpes, (d) allergies, (e) poor skin complexion, esp. acne, or (f) bacterial infections, is effected by contacting the oral and pharyngeal mucosa with 0.022-11 IU/kg of interferon (I) per day.
ADVANTAGE - Admin. as above is the most efficient method of supplying immunotherapeutic amts. of (I) to the lymphatic system.
Dwg.0/0
Dwg.0/0
FS CPI
FA AB
MC CPI: **B02-V03**; B12-A01; B12-A07; B12-D02; B12-D03; B12-D07; B12-D09; B12-G05; B12-G07; B12-L04; **C02-V03**; C12-A01; C12-A07; C12-D02; C12-D03; C12-D07; C12-D09; C12-G05; C12-G07;